Table 6. Representative Raf Inhibitors

Entry	Name
386	3-(2-{[4,6-bis(methyloxy)pyrimidin-2-yl]amino}-1*H*-benzimidazol-5-yl)-2-(3-chloro-2-fluorophenyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one
387	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-(2-{[4-methyl-6-(methyloxy)pyrimidin-2-yl]amino}-1*H*-benzimidazol-5-yl)-2,3-dihydro-1*H*-isoindol-1-one
388	3-hydroxy-2-(3-methylphenyl)-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
389	2-(5-chloro-2-methylphenyl)-3-hydroxy-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
390	methyl {6-[2-(2-fluoro-3-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
391	3-hydroxy-2-[3-(methyloxy)phenyl]-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
392	methyl {6-[(2-{[(2-thienylmethyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
393	methyl {6-[(2-{[(3-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
394	methyl {6-[(2-{[(3-bromophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
395	methyl {6-[(2-{[(3-chlorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
396	methyl {6-[(2-{[(3-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
397	methyl {6-[(2-({[3-(methyloxy)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
398	methyl {6-[(2-({[3-(trifluoromethyl)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
399	methyl {6-[(2-{[(3-ethylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
400	methyl {6-[(2-{[(3-ethynylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
401	methyl {6-[(2-{[(3-chloro-4-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
402	methyl {6-[(2-{[(5-chloro-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
403	methyl {6-[(2-{[(3-iodophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
404	methyl (6-{[2-({[3-(1-methylethyl)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
405	methyl {6-[(2-{[(3-thienylmethyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
406	methyl {6-[(2-{[(3-bromo-4-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
407	methyl {6-[(2-{[(3-chloro-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
408	methyl {6-[(2-{[(4-fluoro-3-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
409	methyl {6-[(2-{[(5-bromo-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
410	methyl {6-[(2-{[(5-bromo-2,4-difluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
411	methyl {6-[(2-{[(5-chloro-2,4-difluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
412	methyl {6-[(2-{[(3-bromo-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
413	methyl {6-[(2-{[(3-ethenylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate

Table 6. Representative Raf Inhibitors	
Entry	Name
414	methyl {6-[(2-{[(3-ethynyl-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
415	methyl {6-[(2-{[(5-chloro-2-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
416	methyl {6-[(2-{[(5-bromo-2-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
417	methyl {6-[(2-{[(2-fluoro-3-iodophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
418	methyl {6-[(2-{[(3-ethenyl-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
419	methyl {6-[(2-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate and
	a single geometric isomer, stereoisomer, racemate, enantiomer, or diastereomer, thereof and optionally as a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Table 7. Representative EGFR and/or VEGFR Inhibitors

Table 7. Representative EGFR and/or VEGFR Inhibitors	
Entry	Name
1	(3*Z*)-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-5-{[1-(phenylmethyl)pyrrolidin-3-yl]amino}-1,3-dihydro-2*H*-indol-2-one
2	(3*Z*)-5-[(1-ethylpiperidin-3-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
3	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
4	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
5	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{[5-(methyloxy)-1*H*-benzimidazol-2-yl][4-(methyloxy)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
6	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
7	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-nitrophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
8	(3*Z*)-3-[1*H*-benzimidazol-2-yl[4-(methyloxy)phenyl]methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
9	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
10	(3*Z*)-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-5-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
11	(3*Z*)-3-[(4-aminophenyl)(1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
12	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
13	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
14	(3*Z*)-5-[(1-ethylpiperidin-4-yl)oxy]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
15	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[4-(methyloxy)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
16	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-fluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one

Table 7. Representative EGFR and/or VEGFR Inhibitors

Entry	Name
17	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
18	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-fluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
19	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-nitrophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
20	3-((*Z*)-1*H*-benzimidazol-2-yl{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}methyl)benzonitrile
21	(3*Z*)-3-[(3-aminophenyl)(1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
22	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-(piperidin-4-ylamino)-1,3-dihydro-2*H*-indol-2-one
23	3-((*Z*)-1*H*-benzimidazol-2-yl{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}methyl)benzenecarboximidamide
24	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
25	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
26	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
27	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
28	2-(2-{2-[(*Z*)-{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}(phenyl)methyl]-1*H*-imidazol-4-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione
29	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-({1-[2-(dimethylamino)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
30	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-({1-(methylsulfonyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
31	(3*Z*)-5-(8-azabicyclo[3.2.1]oct-3-ylamino)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
32	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
33	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
34	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-{[1-(phenylmethyl)piperidin-4-yl]oxy}-1,3-dihydro-2*H*-indol-2-one
35	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
36	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-{[1-[2-(methyloxy)ethyl]piperidin-4-yl}oxy)-1,3-dihydro-2*H*-indol-2-one
37	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-{[1-[2-(methyloxy)ethyl]piperidin-4-yl}oxy)-1,3-dihydro-2*H*-indol-2-one
38	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-{1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
39	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
40	(3*Z*)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
41	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
42	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
43	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)(methyl)amino]-1,3-dihydro-2*H*-indol-2-one

Table 7. Representative EGFR and/or VEGFR Inhibitors

Entry	Name
44	(3Z)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
45	(3Z)-3-[1*H*-benzimidazol-2-yl(4-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
46	(3Z)-3-[1*H*-benzimidazol-2-yl(3-fluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
47	(3Z)-3-[1*H*-benzimidazol-2-yl(4-fluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
48	(3Z)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
49	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
50	(3Z)-3-[1*H*-benzimidazol-2-yl(3-fluoro-4-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
51	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
52	(3Z)-3-[1*H*-benzimidazol-2-yl(4-fluoro-3-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
53	(3Z)-3-[(3-chloro-4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
54	(3Z)-3-[(3,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
55	(3Z)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(phenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
56	(3Z)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
57	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluoro-4-methylphenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
58	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
59	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(4-propylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
60	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[4-(trifluoromethyl)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
61	(3E)-3-[(3,5-difluorophenyl)(5-fluoro-1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
62	(3Z)-3-[(3,5-difluorophenyl)(5-fluoro-1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
63	(3Z)-3-[(3-fluoro-4-methylphenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
64	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-methyl-1*H*-imidazol-2-yl)(4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
65	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[3-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
66	(3Z)-3-[(4-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
67	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluoro-4-methylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
68	(3Z)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[6-(trifluoromethyl)pyridin-3-yl]methylidene}-1,3-dihydro-2*H*-indol-2-one
69	(3Z)-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
70	(3Z)-3-[(3-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one

Table 7. Representative EGFR and/or VEGFR Inhibitors

Entry	Name
71	(3*Z*)-3-{1*H*-imidazol-2-yl[4-(trifluoromethyl)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
72	(3*Z*)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
73	(3*Z*)-3-[(3,5-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
74	(3*Z*)-3-[(3,5-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
75	(3*Z*)-3-[(3,5-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
76	(3*Z*)-3-[(3,5-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
77	(3*Z*)-3-[(4-methyl-1*H*-imidazol-2-yl)(4-methylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
78	(3*Z*)-3-[(4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
79	(3*Z*)-3-[(3,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
80	(3*Z*)-3-[(3-chloro-4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
81	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-(piperidin-4-ylamino)-1,3-dihydro-2*H*-indol-2-one
82	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-piperidin-1-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
83	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-morpholin-4-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
84	(3*Z*)-5-({1-[2-(diethylamino)ethyl]piperidin-4-yl}amino)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
85	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-pyrrolidin-1-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
86	(3*Z*)-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-5-[(1-methylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
87	(3*Z*)-3-[(3-fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
88	ethyl 2-{(*Z*)-(3-fluorophenyl)[5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]methyl}-4-methyl-1*H*-imidazole-5-carboxylate
89	(3*Z*)-3-[1*H*-imidazol-2-yl(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
90	(3*Z*)-3-{1*H*-imidazol-2-yl[4-(methyloxy)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
91	(3*Z*)-3-[(4-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
92	(3*Z*)-3-[[3-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
93	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(methylsulfonyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
94	(3*Z*)-3-[1*H*-imidazol-2-yl(4-propylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
95	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(4-phenyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
96	(3*Z*)-3-[(3-fluorophenyl)(4-phenyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
97	(3*Z*)-3-[(3-fluoro-4-methylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one

Table 7. Representative EGFR and/or VEGFR Inhibitors

Entry	Name
98	(3*Z*)-3-{1*H*-imidazol-2-yl[6-(trifluoromethyl)pyridin-3-yl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
99	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
100	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[2-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
101	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-methyl-1*H*-imidazol-2-yl)[4-(trifluoromethyl)phenyl]methylidene]-1,3-dihydro-2*H*-indol-2-one
102	(3*Z*)-3-[(4-chlorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
103	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[3-fluoro-4-(trifluoromethyl)phenyl](4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
104	(3*Z*)-3-[(3,4-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
105	(3*Z*)-3-[(3-chloro-4-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
106	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
107	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(2-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
108	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[2-fluoro-4-(trifluoromethyl)phenyl](4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
109	(3*Z*)-3-[(2,3-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
110	(3*Z*)-3-[(2,3-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
111	(3*Z*)-3-[(2,4-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
112	(3*Z*)-3-[(2,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
113	(3*Z*)-3-[(2-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
114	(3*Z*)-3-[(3-trifluoromethylphenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
115	(3*Z*)-3-[(3-trifluoromethylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
116	(3*Z*)-3-[(2,4-dichloro-5-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
117	(3*Z*)-3-[(2,4-dichloro-5-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
118	(3*Z*)-3-[(4-chloro-2-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one and
	a single geometric isomer, stereoisomer, racemate, enantiomer, or diastereomer, thereof and optionally as a pharmaceutically acceptable salt, solvate, or hydrate thereof.

General Administration

[00251] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of MEK according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other embodiments, administration

may preferably be by the oral route. Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[00252] The compositions can include a conventional pharmaceutical carrier, excipient, and/or adjuvants and a compound of Formula I, and, in addition, may include other medicinal agents and pharmaceutical agents that are generally administered to a patient being treated for cancer.

[00253] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00254] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[00255] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix

of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[00256] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[00257] One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[00258] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[00259] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00260] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00261] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[00262] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[00263] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations,

eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[00264] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[00265] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[00266] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[00267] The compounds of the invention, or their pharmaceutically acceptable salts or hydrates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[00268] If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other

pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

[00269] Representative pharmaceutical formulations containing a compound of Formula I are described below in the Pharmaceutical Composition Examples.

UTILITY

[00270] Certain compounds of Formula I have been tested using the assay described in Biological Example 1 and have been determined to be MEK inhibitors. As such, compounds of Formula I are useful for treating diseases, particularly cancer in which MEK activity contributes to the pathology and/or symptomatology of the disease. For example, cancer in which MEK activity contributes to its pathology and/or symptomatology include malignant melanomas, colon cancer, rectal cancer, pancreatic cancer, lung cancer, papillary and anaplastic thyroid cancer, and endometrial cancer, ovarian cancer, and the like.

[00271] Suitable *in vitro* assays for measuring MEK activity and the inhibition thereof by compounds are known in the art. For example, see WO 2006/061712 for measuring MEK1 and MEK2 *in vitro*. For further details of an *in vitro* assay for measuring MEK activity see Biological Examples, Example 1 *infra*. Following the examples disclosed herein, as well as those disclosed in the art, a person of ordinary skill in the art can determine the inhibitory activity of a compound of this invention.

[00272] Assays for measurement of *in vitro* efficacy in treatment of cancer are known in the art. For example, see WO 2006/061712, which is herein incorporated by reference, for cell-based assays for colon cancer. In addition, cell-based tumor models are described in Biological Examples, Example 2 and 3 *infra*.

[00273] Suitable *in vivo* models for cancer are known to those of ordinary skill in the art (including WO 2006/061712). For further details of *in vivo* models for colorectal cancer, melanoma, breast adenocarcinoma, and lung anaplastic carcinoma, see Biological Examples 4 and 5, *infra*. Biological Example 5 describes a particular combination of treatments. In conjunction with what is known in the art, one of ordinary skill in the art would know how to follow these examples to test other combinations of treatments.

General Synthesis

[00274] Compounds of this invention can be made by the synthetic procedures described below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[00275] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

[00276] Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups regenerate original functional groups by routine manipulation or *in vivo*. Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association

and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[00277] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds of Formula I that may be prepared through the syntheses described herein may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention. Some of the compounds of the invention may exist as tautomers. For example, where a ketone or aldehyde is present, the molecule may exist in the enol form; where an amide is present, the molecule may exist as the imidic acid; and where an enamine is present, the molecule may exist as an imine. All such tautomers are within the scope of the invention.

[00278] The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

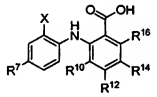
[00279] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and

unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[00280] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[00281] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art.

[00282] An intermediate of Formula II:

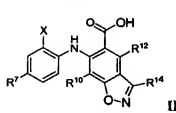


II

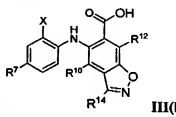
where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group A can be prepared using procedures known to one of ordinary skill in the art. In particular, see (for example) US 7,019,033, WO 2002006213, WO 2003062191, WO 2003062189, WO 2002018319, WO2001005392, WO 2000064856, WO 2001005392, WO 9901421, WO 2004056789, Davis, E. M. et al. *Org. Process Res. & Dev.* **2005**, 9, 843-6, and Shapiro, N. *et al. Synthetic Commun.* **2005**, 35, 2265-9 which are incorporated by reference herein. The following intermediates were prepared using similar procedures as described in the above references: 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid; 2-[(2-chloro-4-iodophenyl)amino]-3,4-difluorobenzoic acid; 4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid;

4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid; and 2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorobenzoic acid.

[00283] An intermediate of Formula III(a) or III(b):



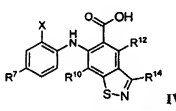
III(a);



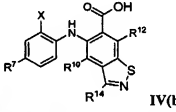
III(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular for formula III(a), where R^{14} is amino or alkyl (particularly methyl); R^{10} is halo (particularly fluoro); R^7 is hydrogen or halo (particularly bromo or chloro); X is halo (particularly chloro); and R^{12} is hydrogen see for example WO2006030610, US2005049419, and US2005/0054701 which are incorporated by reference herein. 6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-1,2-benzisoxazole-5-carboxylic acid was prepared using methods similar to those disclosed in WO2006030610, US2005049419, and US2005/0054701.

[00284] An intermediate of Formula IV(a) or IV(b):



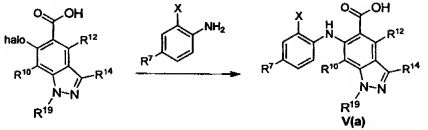
IV(a);



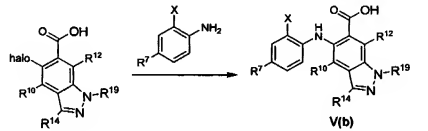
IV(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art.

[00285] An intermediate of Formula V(a) or V(b):



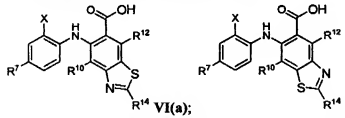
V(a)



V(b)

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular the halo precursor of V(a) can be prepared using, for example, WO2003101968 and WO2002083648 which are incorporated by reference herein. In particular the halo precursor of V(b) can be prepared using, for example, US2004192653, US2004180896, US2004176325 which are incorporated by reference herein. The halo precursors are then reacted with an appropriate aniline to yield the intermediates of Formula V(a) and V(b).

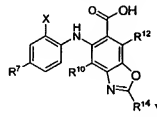
[00286] An intermediate of Formula VI(a) or VI(b):



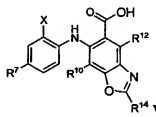
VI(a); VI(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, for VI(b) see for example WO2000042022 and WO2001005390 which are incorporated by reference herein.

[00287] An intermediate of Formula VII(a) or VII(b):



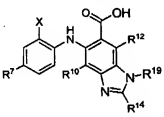
VII(a);



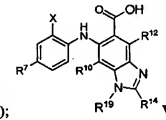
VII(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. For intermediate VII(b) see, for example, WO2001005390 and WO2000042022 which are incorporated by reference herein.

[00288] An intermediate of Formula VIII(a) or VIII(b):



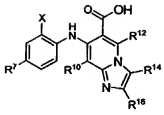
VIII(a);



VIII(b)

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular for formula VIII(b) where R^{10} is halo (particularly fluoro), R^{12} is hydrogen, R^{14} is hydrogen, and R^{19} is hydrogen or alkyl (particularly methyl) or alkenyl (particularly allyl), see WO 05/023251, WO2005009975, and WO2001005390 which are incorporated by reference herein. In particular for VIII(a) where X is halo (particularly chloro or fluoro) or alkyl (particularly methyl), R^7 is halo (particularly iodo, bromo, or chloro) or haloalkoxy (particularly trifluormethoxy), R^{10} is halo (particularly fluoro or chloro), R^{14} is hydrogen or alkyl (particularly methyl), and R^{19} is hydrogen or alkyl (particularly methyl), see for example US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, and WO2001005390 which are incorporated by reference herein. The following intermediates were prepared using similar procedures described in US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, and WO2001005390: 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazole-6-carboxylic acid and 4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazole-6-carboxylic acid.

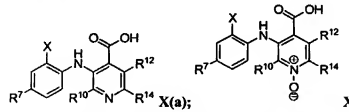
[00289] An intermediate of Formula IX:



IX

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen or halo (particularly chloro or fluoro); R^{12} is hydrogen; R^{14} is hydrogen, amino, alkylamino, or dialkylamino; R^{16} is hydrogen; X is halo (particularly chloro); and R^7 is halo (particularly bromo) see for example WO 05/023759, US 2005/0054701, US 2006030610, US 2005049419, and US 2005049276 which are incorporated by reference herein. The following intermediates were prepared using similar procedures as those described in WO 05/023759, as well as US 2006030610 and US 2005/0054701: 7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridine-6-carboxylic acid and 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridine-6-carboxylic acid. The following intermediates can be prepared using similar procedures described in the references given above: 8-Fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid and 7-[(4-Bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridine-6-carboxylic acid.

[00290] An intermediate of Formula X(a) and X(b):

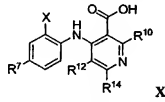


X(a); X(b)

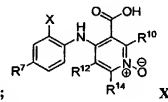
where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen, halo (specifically chloro), or alkyl (specifically methyl), R^{12} is hydrogen, and R^{14} is hydrogen, halo (specifically bromo), see for example WO 06/045514 which is incorporated by reference herein. To prepare the intermediate of Formula X(b), the nitrogen in the pyridine ring of X(a) can then be oxidized with an agent such as MCPBA or H_2O_2. The following X(a) and X(b)

intermediates were prepared using similar methods as disclosed in WO 06/045514: 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid and 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid 1-oxide. The following X(a) intermediates can be prepared using similar methods as disclosed in WO 06/045514: 2-Fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid and 3-[(4-Bromo-2-fluorophenyl)amino]pyridine-4-carboxylic acid.

[00291] An intermediate of Formula XI(a):



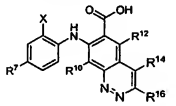
XI(a);



XI(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen, R^{12} is hydrogen or halo (particularly chloro or fluoro), R^{14} is amino or halo (particularly chloro), X is halo (particularly chloro), and R^7 is halo (particularly bromo) see for example US 2005/0054701, US 200549419, and US 2006030610 which are incorporated by reference herein. The intermediate of Formula XI(b) can be prepared by oxidizing the nitrogen in the pyridine ring of XI(a) with an agent such as MCPBA or H_2O_2.

[00292] An intermediate of Formula XII:



XII

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 05/051302 which is incorporated by reference herein. The following intermediates can be prepared using similar methods as disclosed in WO 05/051302:

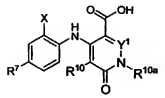
8-Fluoro-7-[(2-fluoro-4-iodophenyl)amino]-4-methylcinnoline-6-carboxylic acid;

7-[(4-Bromo-2-chlorophenyl)amino]-8-fluoro-4-methylcinnoline-6-carboxylic acid;

7-[(4-Bromo-2-fluorophenyl)amino]-8-fluoro-4-methylcinnoline-6-carboxylic acid; and

7-[(4-Bromo-2-fluorophenyl)amino]cinnoline-6-carboxylic acid.

[00293] An intermediate of Formula XIII:



XIII

where R^7, X, R^{10}, R^{10a}, and Y^1 are as defined in the Summary of the Invention for Group C can be prepared using procedures known to one of ordinary skill in the art, including for example the procedures in US 05/0256123, Wallace, E. M. *et al. J. Med. Chem.* **2006**, 49, 441-4, WO 2005000818, and WO 2005051301 (where Y^1 is carbon) which are incorporated by reference herein. 4-[(4-Bromo-2-fluorophenyl)amino]-5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid was prepared using similar procedures to those disclosed in US 05/0256123 and WO 2005051301. 4-Chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid was prepared using similar procedures to those disclosed in US 2005256123.

The following intermediates can be prepared using the methods disclosed in the above references:

4-[(2-Fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

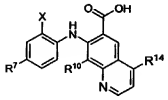
4-[(4-Bromo-2-fluorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-5-fluoro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid; and

4-[(4-Bromo-2-fluorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid.

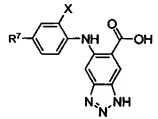
[00294] An intermediate of Formula XIV:



XIV

where R^7, X, R^{10}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 05/051302 which is incorporated by reference herein.

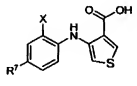
[00295] An intermediate of Formula XVI



XVI

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 2001005390 and WO 2000042022 for procedures that can be used to prepare the following: 5-[(2-Fluoro-4-iodophenyl)amino]-1*H*-benzotriazole-6-carboxylic acid; 5-[(2-Fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzotriazole-6-carboxylic acid; and 4-Fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-benzotriazole-6-carboxylic acid.

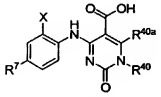
[00296] An intermediate of Formula XVII



XVII

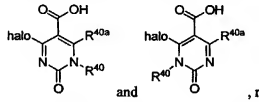
where X and R^7 are as defined in the Summary of the Invention for a Compound of Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see Example 29.

[00297] An intermediate of Formula XVIII(a) or XVIII(b)



XVIII(a) **XVIII(b)**

where X, R^7, R^{40}, and R^{40a} are as defined in the Summary of the Invention for a Compound of Group D can be prepared using procedures known to one of ordinary skill in the art. In particular, the halo precursors to XVIII(a) and XVIII(b)

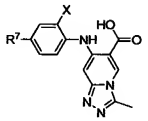


and , respectively

can be prepared using procedures similar to those described in Machon and Dlugosz *Acta Poloniae Pharmaceutica* **1983,** *40(1),* 1-6 and von Angerer, *Science of Synthesis* **2004,** *16,* 379-572 (General Review written in English). The halo precursors are then reacted with

using procedures known to one of ordinary skill in the art and the synthetic methods disclosed herein. The following intermediates can be prepared as described above: 6-[(2-fluoro-4-iodophenyl)amino]-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid and 4-[(2-fluoro-4-iodophenyl)amino]-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid.

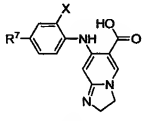
[00298] An intermediate of Formula XIX



XIX

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group C can be prepared using methods known to one of ordinary skill in the art. In particular see US 2005049276.

[00299] An intermediate of Formula XX

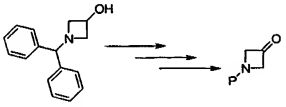


XX

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group C can be prepared using methods known to one of ordinary skill in the art. In particular see US 2005049276.

[00300] The synthesis of azetidines substituted at the 3-position can be conveniently carried out according to Scheme 1:

Scheme 1



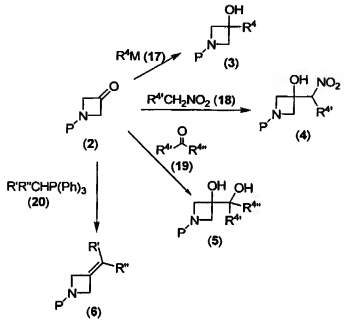
(1) (2)

starting from the *N*-diphenylmethyl protected azetidin-3-ol (**1**), readily prepared by reaction of epichlorohydrin and diphenylmethylamine (Chatterjee, Shym S.; Triggle, D. *J. Chemical Communications (London)* **1968**, *2*, 93). Protecting group exchange, from Boc to CBz, on the azetidine is carried out according to literature protocols (Greene, T.W., Wuts, P.G. Protective Groups in Organic Synthesis, Wiley-

Interscience) and subsequent oxidation to the azetidinone (**2**) where P is CBz provides a useful intermediate for the preparation of compounds of the invention.

[00301] For example, the ketone intermediates of formula **2** can be broadly functionalized at the 3-position according to Scheme 2.

Scheme 2

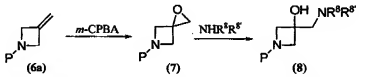


An intermediate of formula (**3**), where R^4 is as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D can be prepared by reacting the intermediate **2** with Grignard reagents or other organometallic species of formula **17**, such as organolithiums. Alternatively, the intermediate **2** can be reacted with nitroalkane anions of formula **18** prepared *in-situ* as in the Henry reaction (The Henry reaction, recent examples: Luzzio, F. A. *Tetrahedron* **2001**, *57(6)*, 915-945) to give (**4**) where $R^{4'}$ is hydrogen or alkyl optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D. Alternatively, the intermediate **2** can be reacted with ketone or aldehyde anions of formula **19** in a Claisen-type condensation to give (**5**) where $R^{4'}$ is alkyl optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D and $R^{4''}$ is hydrogen or $R^{4'}$. In addition, **2** can be reacted with Wittig reagents of formula **20** (where R' and R" are independently hydrogen, alkyl,

alkenyl, aryl, or heteroaryl and the alkyl, alkenyl, aryl, and heteroaryl are optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D) to prepare intermediates of formula 6, which are also useful as precursors for compounds of the invention.

[00302] According to Scheme 3, intermediates of formula (6) where where (R' and R" are hydrogen and P is a nitrogen-protecting group such as CBz or Boc)

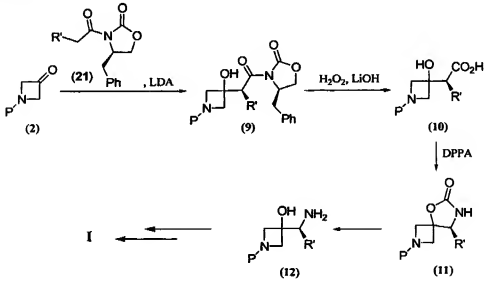
Scheme 3



can be further converted to the corresponding epoxide (7) and subsequent reaction with a suitable nitrogen base or other nucleophiles may be carried out to give access to a broad range of azetidin-3-ol derivatives such as (8), where R^8 and $R^{8'}$ are as defined in the Summary of the Invention.

[00303] In some cases the preparation of optically pure compounds is desired where the azetidine contains one or more stereocenters. Numerous techniques for the preparation of optically pure compounds through both resolution techniques and asymmetric synthesis are well known in the art. In one such case, an asymmetric synthesis methodology can be employed where an azetidine precursor of formula (2) is reacted with an intermediate of formula 21 where R' is not hydrogen, as depicted in Scheme 4.

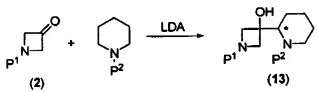
Scheme 4



One such useful approach makes use of Evans oxazolidinone methodology (Diastereoselective aldol condensation using a chiral oxazolidinone auxiliary. Gage, James R.; Evans, David A. *Organic Syntheses* **1990**, *68*, 83-91). The condensation of an azetidinone (**2**) with the a chiral oxazolidinone in the presence of a base such as LDA affords an intermediate oxazolidinone (**9**), where P is a nitrogen-protecting group such as CBz or Boc, with diastereoselectivity. Treatment with lithium hydroxide in aqueous hydrogen peroxide gives carboxylic acid (**10**) which can be subject to Curtius rearrangement to provide the chiral oxazolidinone (**11**) then carried forward as required to a useful intermediate (**12**). Further protecting group manipulation and derivatization as required can be employed to prepare compounds of Formula I.

[00304] Alternatively, a racemic mixture of an intermediate of formula (**13**), useful to prepare a compound of Formula I where R^3 is hydroxy and R^4 is heterocycloalkyl (in particular, where R^4 is a N-protected piperidine), can be prepared according to Scheme 5.

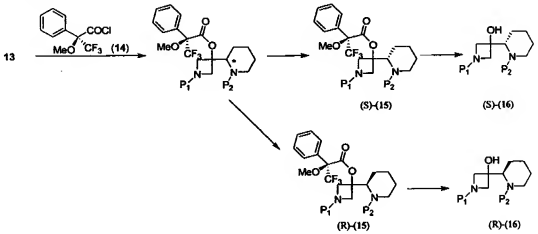
Scheme 5



(2) (13)

In the reaction schemes P^1 and P^2 are orthogonal nitrogen-protecting groups. For example, P^1 is Boc and P^2 is CBz or P^1 is CBz and P^2 is Boc. The reaction is carried out *in-situ* by treating **22** to generate the lithated amine and by subsequently treating it with a ketone such as (**2**) according to the method of Peter Beak (Beak, Peter; Lee, Won Koo α-Lithioamine synthetic equivalents: syntheses of diastereoisomers from the Boc-piperidines. Journal of Organic Chemistry 1990, 55(9), 2578-80). The racemate (**13**) thus prepared can be resolved by functionalization, as depicted in Scheme 6, with a chiral acid such as the readily-available Mosher acid (**14**).

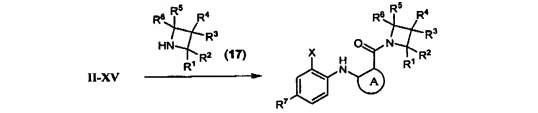
Scheme 6



The resulting diastereomeric esters (**15**) can be separated by chromatographic means and then carried forward individually as the enantiomerically pure intermediates (R)-(**16**) and (S)-(**16**).

[00305] Compounds of the Invention can be prepared by reacting an intermediate of Formula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, or XX with intermediate 17 according to Scheme 7:

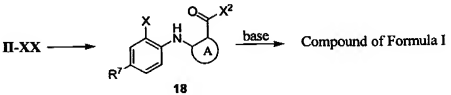
Scheme 7



The reaction is carried out in a solvent such as DMF, THF, or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, DMAP, or triethylamine and optionally in the presence of a coupling agent such as PyBOP, HBTU, or EDCI.

[00306] Alternatively an intermediate of Formula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, or XX can be converted into an acid halide according to Scheme 8

Scheme 8



18

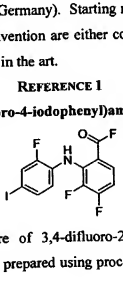
where X^2 is halo, such as chloro or fluoro, and all other groups are as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D. The reaction is carried out in a solvent such as dioxane, THF, or DCM in the presence of a base such as DIPEA, sodium bicarbonate. The acid halide of formula **18** can then be reacted with an azetidine intermediate of formula **17** to prepare a compound of Formula I.

SYNTHETIC EXAMPLES

[00307] Generally, the compounds listed below were identified by LC-MS, and/or isolated, and characterized by ^{1}H-NMR (most typically 400 MHz). Liquid chromatography-mass spectral (LC-MS) analyses were performed using at least one of: a Hewlett-Packard Series 1100 MSD, an Agilent 1100 Series LC/MSD (available from Agilent Technologies Deutschland GmbH of Waldbronn Germany), or a Waters 8-Channel MUX System (available from Waters Corporation of Milford, Massachusetts). Compounds were identified according to either their observed mass [MH^+] or [MNa^+] ion (positive mode) or [MH^-] ion (negative mode). ^{1}H-NMR data for compounds was taken with a Varian AS400 Spectrometer (400MHz, available from Varian GmbH, Darmstadt, Germany). Starting materials and intermediates used to prepare a compound of the invention are either commercially available or can be prepared by one of ordinary skill in the art.

REFERENCE 1

3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride

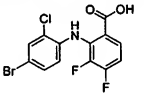


[00308] To a stirred mixture of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoic acid (12 g, 30.5 mmol), prepared using procedures similar to those described

in US 7,019,033, in dichloromethane (70 mL) at 0 °C was added pyridine (2.5 mL, 30.8 mmol) followed by dropwise addition of cyanuric fluoride (2.8 mL, 33.6 mmol). The reaction mixture was stirred at 0 °C for 10 minutes and then warmed to room temperature and stirred for 2 hours. The reaction mixture was diluted with water and extracted with dichloromethane (100 mL). The aqueous layer was extracted once with dichloromethane (50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude product as a brownish solid. Crude product was purified by flash chromatography (plug, 25% ethyl acetate in hexanes) to afford 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride as a beige solid (11.8 g, 97% yield). ^{1}H NMR (400MHz, CD_3OD): 8.41 (s, 1H), 7.80-7.81 (m, 1H), 7.52 (dd, 1H), 7.43-7.47 (m, 1H), 6.96-7.03 (m, 1H), 6.85-6.92 (m, 1H).

REFERENCE 2

2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorobenzoic acid

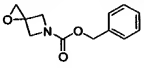


[00309] To a solution of 2,3,4-trifluorobenzoic acid (1 g, 5.68 mmol) and 4-bromo-2-chloroaniline (1.2 g, 5.68 mmol) in acetonitrile (10 mL) was added lithium amide (0.39 g, 17.04 mmol) and the reaction stirred at 60 °C for 1.5 hours. The mixture was cooled to room temperature and then to 0 °C and acidified with aq. hydrochloric acid. The obtained precipitate was collected by filtration and washed with cold water and dried *in vacuo* to afford 2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorobenzoic acid (1.92 g, 94% yield) as a beige solid. MS (EI) for $C_{13}H_7BrClF_2NO_2$: 363 (MH^+).

[00310] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, 2-[(4-iodo-2-fluorophenyl)amino]-3-fluorobenzoic acid was prepared. MS (EI) for $C_{13}H_8F_2INO_2$: 376 (MH^+).

REFERENCE 3

Phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate



[00311] To a solution of azetidin-3-ol hydrochloride in tetrahydrofuran (90 mL) and water (10 mL) was added triethylamine (15 mL, 0.106 mol) followed by slow addition of benzyl chloroformate (8.0 mL, 0.056 mol) at room temperature. The reaction mixture was stirred at room termperature for 16 hours then partitioned with water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (SiO_2, 25-50% ethyl acetate in hexanes) to afford phenylmethyl 3-hydroxyazetidine-1-carboxylate (3.56 g, 33% yield) as a clear and colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 7.36-7.31 (m, 5H), 5.09 (s, 2H), 4.64-4.57 (m, 1H), 4.22 (dd, 2H), 3.88 (dd, 2H), 2.61 (d, 1H, J=4.0 Hz). MS (EI) for $C_{11}H_{13}NO_3$: 208 (MH^+).

[00312] To a solution of phenylmethyl 3-hydroxyazetidine-1-carboxylate (3.5 g, 0.0168 mol) in dichloromethane (100 mL) was added Dess-Martin periodinane (10.7 g, 0.0.25 mol) at room temperature and stirred for 5 h. The reaction mixture was quenched with 1:1 ratio of saturated aqueous sodium bicarbonate and 1M sodium thiosulfate (200 mL) and then partitioned with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford phenylmethyl 3-oxoazetidine-1-carboxylate (3.43 g, 99% yield) as a clear and colorless oil without further purification. ^1H NMR (400 MHz, $CDCl_3$): 7.39-7.31 (m, 5H), 5.17 (s, 2H), 4.77 (s, 4H). MS (EI) for $C_{11}H_{11}NO_3$: 205 (M^+).

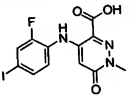
[00313] A suspension of methyltriphenylphosphonium bromide (23.0 g, 0.0649 mol) and potassium *tert*-butoxide (7.3 g, 0.0649 mol) in diethyl ether (140 mL) was stirred at room temperature for 20 min, and then heated to 35 °C for 1 h. To this bright yellow reaction mixture was slowly added a dilute solution of phenylmethyl 3-oxoazetidine-1-carboxylate (3.33 g, 0.0162 mol) in diethyl ether (50 mL). The reaction mixture was stirred at 35 °C for 12 hours then filtered through a bed of celite and rinsed with ethyl ether. The filtrate was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (SiO_2, 5-10% ethyl acetate in hexanes) to afford phenylmethyl 3-methylideneazetidine-1-carboxylate (2.46 g, 75% yield) as a clear and colorless oil). ^1H NMR (400 MHz, $CDCl_3$): 7.27-7.22 (m, 5H), 5.02 (s, 2H), 4.93-4.90 (m, 2H), 4.48-4.47 (m, 4H). MS (EI) for $C_{12}H_{13}NO_2$: 203 (M^+).

[00314] To a solution of phenylmethyl 3-methylideneazetidine-1-carboxylate (2.46 g, 0.0121 mol) in chloroform (100 mL) was added 3-chloroperoxybenzoic acid (12.5 g, 0.0726 mol) at 0 °C. The reaction mixture was allowed to warm up to room

temperature over a period of 12 hours then quenched with 1 M sodium thiosulfate / saturated aqueous sodium bicarbonate (1:1). The layers were separated and the organic layer was dried over anhydrous magnesium sulfate then concentrated. The residue was purified by flash chromatography (5-15% ethyl acetate in hexanes) to afford phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (2.2 g, 83% yield) as clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.29 (m, 5H), 5.12 (s, 2H), 4.35-4.26 (m, 4H), 2.85 (s, 2H). MS (EI) for $C_{12}H_{13}NO_3$: 220 (MH^+).

REFERENCE 4

4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid



[00315] 4-chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid was prepared using procedures similar to those disclosed in US 2005256123.

[00316] To a solution of 4-chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (350 mg, 1.855 mmol) and 2-fluoro-4-iodoaniline (1.06 g, 4.453 mmol) in tetrahydrofuran (13.3 mL) was sparged with nitrogen for 5 minutes followed by the slow addition of lithium bis(trimethylsilyl)amide, 1.0 M in THF (7.4 mL). The reaction mixture stirred for an additional 4 hours at room temperature. The mixture was quenched with 1 N HCl and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 N aqueous HCl. The aqueous layer was extracted (3x) with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to afford 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (939 mg, 100% yield). ^{1}H NMR ($CDCl_3$): 7.27 (dd, 1H), 7.21 (d, 1H), 6.54 (t, 1H), 4.84 (broad s, 2H), 2.09 (s, 1H), 1.26 (t, 3H); MS (EI) for $C_{12}H_9N_3O_3FI$: 389 (MH^+).

[00317] A solution of 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (939 mg, 2.413 mmol) in dichloromethane (60 mL) in the presence of dimethylformamide (8.0 mL) was cooled to 0 °C. Malonyl chloride (1.26 mL, 14.48 mmol) was added and stirred at room temperature

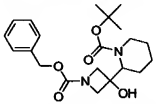
for 1 hour. The reaction mixture was evaporated and partitioned between ethyl acetate and 1M aqueous ammonium chloride. The aqueous layer was extracted 1x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carbonyl chloride. This crude material was taken into the next step without further purification. MS (EI) for $C_{12}H_8N_3O_2ClFI$: 408 (MH^+).

[00318] To a solution of 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carbonyl chloride in methanol (15 mL) and benzene (12 mL) was added dropwise trimethylsilyl diazomethane (1 mL) and stirred at room temperature for 15 minutes. The reaction mixture was quenched with acetic acid and evaporated. The residue was partitioned between ethyl acetate and brine. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified on silica gel chromatography column (7:3 hexanes/ethyl acetate) to afford methyl 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (84.9 mg, 8.7% yield). ^1H NMR ($CDCl_3$): 7.49-7.56 (m, 3H), 7.12 (t, 1H), 6.13 (d, 1H), 4.00 (s, 3H), 3.83 (s, 3H); MS (EI) for $C_{13}H_{11}N_3O_3FI$: 404 (MH^+).

[00319] Methyl 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (84.9 mg, 0.211 mmol) was dissolved in tetrahydrofuran (5 mL), methanol (2.5 mL) and water (2.5 mL). Aqueous 2 M lithium hydroxide (200 μL) was added at room temperature. After 10 minutes, the reaction mixture was heated to 50 °C for 30 minutes and continued to stir at room temperature for 16 hours at which time the solvents were evaporated. The residue was made acidic with 2 M aqueous hydrochloric acid to pH 2 and extracted with ethyl acetate. The organic layer separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (54.0 mg, 66% yield). MS (EI) for $C_{12}H_9N_3O_3FI$: 390 (MH^+).

REFERENCE 5

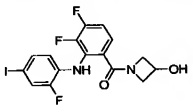
1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate



[00320] To a solution of 1,1-dimethylethyl piperidine-1-carboxylate (0.50 g, 2.7 mmol) in anhydrous diethyl ether (9.0 mL) under anhydrous nitrogen gas was added *N,N,N',N'*-tetramethylethane-1,2-diamine (0.41 mL, 2.7 mmol), and the solution was cooled to -78°C. To this solution was added (2-methylpropyl)lithium (2.1 mL, 1.4 M in cyclohexane, 3.0 mmol) in small portions. To this anion solution was added phenylmethyl 3-oxoazetidine-1-carboxylate (1.0 g, 5.4 mmol), prepared using procedures as described in Reference 3, in anhydrous ether (2.0 mL), while maintaining the internal temperature at less than -60°C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water, and partitioned between water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether twice. The combined organic layers were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Chromatography (silica gel, 3:1 hexanes/ethyl acetate) gave 0.13 g (13%) of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (m, 5H), 5.08 (s, 2H), 4.05 (d, 1H), 4.00 (d, 1H), 3.84 (d, 2H), 3.80 (broad s, 1H), 3.55 (broad s, 1H), 3.10 (broad s, 1H), 1.92 (m, 1H), 1.45-1.62 (m, 6H), 1.43 (s, 9H). MS (EI) for $C_{21}H_{30}N_2O_5$: 335 (M-tBu), 315 (M-OtBu).

EXAMPLE 1

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00321] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (2.1 g, 5.3 mmol), prepared using procedures similar to those in US 7,019,033, was taken into DMF (10 mL) followed by addition of PyBOP (2.6 g, 5.3 mmol) and the mixture was allowed to stir at room temperature over 15 minutes. Azetidin-3-ol hydrochloride (870 mg, 8.0 mmol) and DIPEA (1.85 mL, 11.2 mmol) was then added and the mixture was allowed to stir an additional hour at room temperature. The mixture was then partitioned with ethyl acetate and 0.5 M aqueous sodium hydroxide solution. The organic layer was then washed with water (3x) then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography using ethyl acetate: hexanes (5:1) eluent afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (2.09 g, 87% yield) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (s, 1H), 7.39 (dd, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.78 (m, 1H), 6.63-6.57 (m, 1H), 4.74-4.67 (m, 1H), 4.43-4.39 (m, 2H), 4.20-3.96 (br d, 2H), 2.50 (d, 1H).

[00322] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the compounds in Examples 1(a)-(e) were prepared.

EXAMPLE 1(a). 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}-carbonyl)azetidin-3-yl]-*N,N*-dimethylpyrrolidin-3-amine. The title compound was prepared by reacting 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid with *N*-methyl-*N*-(2-(pyridin-2-yl)ethyl)azetidin-3-amine. The azetidine intermediate was prepared using procedures similar to those described in Abdel-Magid, et.al., *Tetrahedron Letters* **1990,** *31(39),* 5595 starting with *tert*-butyl 3-oxoazetidine-1-carboxylate, which itself was prepared as described in Example 3. The title compound: ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (s, 1H), 7.58 (m, 1H), 7.38 (d, 1H), 7.31 (m, 1H), 7.16 (m, 1H), 6.67 (m, 1H), 4.16 (m, 1H), 3.97 (m, 2H), 3.77 (m, 1H), 3.26 (br s, 4H), 2.63 (m, 1H), 2.42 (br s, 6H), 1.99 (br s, 1H), 1.74 (br s, 1H). MS (EI) for $C_{22}H_{24}F_3IN_4O$: 545 (MH^+).

EXAMPLE 1(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methyl-*N*-(2-pyridin-2-ylethyl)azetidin-3-amine. The title compound was prepared by reacting 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid with 1-(azetidin-3-yl)-N,N-dimethylpyrrolidin-3-amine. The azetidine intermediate was preparedusing procedures similar to those described in Abdel-Magid, et.al., *Tetrahedron Letters* **1990,** *31(39),* 5595 starting

with *tert*-butyl 3-oxoazetidine-1-carboxylate, which itself was prepared as described in Example 3. The title compound: ^{1}H NMR(400 MHz, CD_3OD): 8.50 (d, 1H), 7.94 (t, 1H), 7.50-7.30 (m, 5H), 7.07 (q, 1H), 6.66- 6.61 (m, 1H), 4.52-4.48 (m, 2H), 4.31(s, 2H), 4.23-4.18 (m, 1H), 3.48- 3.46 (m, 2H), 3.17-3.13 (m, 2H), 2.88 (s, 3H); MS(EI) for $C_{24}H_{22}F_3IN_4O$: 567 (MH^+).

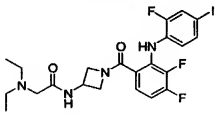
EXAMPLE 1(c). 6-(Azetidin-1-ylcarbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline: ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.31 (dt, 1H), 7.13-7.09 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.27 (b, 2H), 4.18 (b, 2H), 2.38-2.30 (p, 2H); MS (EI) for $C_{16}H_{12}F_3IN_3O$: 433 (MH^+).

EXAMPLE 1(d). [1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.31 (dt, 1H), 7.15-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.29-4.20 (m, 2H), 4.09 (b, 1H), 3.93 (b, 1H), 3.82-3.81 (d, 2H), 2.89-2.75 (m, 1H); MS (EI) for $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

EXAMPLE 1(e). 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (b, 2H), 7.42-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.15-7.11 (m, 1H), 6.89-6.83 (m, 1H), 6.65-6.60 (m, 1H), 4.46-4.29 (m, 4H), 3.55-3.47 (m, 1H); MS (EI) for $C_{17}H_{12}F_3IN_2O_3$: 477 (MH^+).

EXAMPLE 2

_N_-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-_N2,N2_-diethylglycinamide



[00323] A solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (200 mg, 0.51 mmol), prepared using procedures similar to those in US 7,019,033, PyBOP (256 mg, 0.51 mmol), commercially available *tert*-butyl azetidin-3-ylcarbamate (131 mg, 0.77 mmol) and *N,N*-diisopropylethylamine (180 μL, 1.02 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 15 hours. The reaction mixture was partitioned between 5% aqueous lithium chloride and ethyl

acetate. The organic portion was washed with 20% aqueous citric acid, saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexanes to afford 1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (225 mg, 80% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.60-7.55 (m, 2H), 7.38 (d, 1H), 7.30-7.26 (m, 1H), 7.20-7.13 (m, 1H), 6.71-6.66 (m, 1H), 4.37-4.20 (m, 2H), 4.18-4.06 (m, 1H), 3.98-3.93 (m, 1H), 3.82-3.75 (m, 1H), 1.37 (s, 9H). MS (EI) $C_{21}H_{21}N_3O_3F_3I$: 548 (MH^+).

[00324] A solution of 1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (113 mg, 0.20 mmol) and trifluoroacetic acid (500 μL) in dichloromethane (2 mL) was added stirred at room temperature for one hour then was partitioned between saturated aqueous sodium bicarbonate, and dichloromethane. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford a colorless residue which was purified by column chromatography eluting with 10% methanol in dichloromethane to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (85 mg, 95% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.46-4.39 (m, 2H), 3.98-3.75(br m, 4H); MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

[00325] A solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (100 mg, 0.22 mmol), PyBOP (131 mg, 0.25 mmol), *N,N*-diisopropylethylamine (80 μL, 0.44 mol) and bromoacetic acid (35 mg, 0.25 mmol) in dimethylformamide (1 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and the resultant residue was purified by column chromatography eluting with 80% ethyl acetate in hexanes to afford 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]acetamide (102 mg, 82% yield) as a white foam. MS (EI) for $C_{18}H_{14}BrF_3IN_3O_2$: 568.

[00326] A solution of 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]acetamide (30 mg, 0.05 mmol) and

N,N-diethylamine (100 μL, excess) in dichloromethane (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and purified by preparative reverse phase HPLC (CH_3CN/H_2O with 0.1% TFA). Isolated product was concentrated *in vacuo* to afford *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N2,N2*-diethylglycinamide trifluoroacetate salt (13.0 mg, 38% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 9.36 (br s, 1H), 9.25 (d, 1H), 8.60 (s, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 7.33-7.27 (m, 1H), 7.22-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.54-4.40 (m, 2H), 4.25-4.20 (m, 1H), 4.04-3.82 (m, 4H), 3.17-3.12 (m, 4H), 1.18-1.15 (m, 6H); MS (EI) $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

[00327] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the compounds in Examples 2(a)-(n) were prepared.

EXAMPLE 2(a). 1,1-Dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (br s, 1H), 7.40 (dd, 1H), 7.33 (dt, 1H), 7.13-7.07 (m, 1H), 6.80 (ddd, 1H), 6.61 (ddd, 1H), 5.01-4.88 (br, 1H), 4.55-4.37 (br, 4H), 4.05 (br d, 1H), 1.43 (s, 9H); MS (EI) for $C_{21}H_{21}F_3IN_3O_3S$: 548 (MH^+).

EXAMPLE 2(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine trifluoroacetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.46-4.39 (m, 2H), 3.98-3.75(br m, 4H); MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 2(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-methylpropanamide: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 8.38 (d, 1H), 7.59 (d, 1H), 7.38 (d, 1H), 7.32-7.28 (m, 1H), 7.18-7.13 (m, 1H), 6.72-6.66 (m, 1H), 4.45-4.35 (m, 1H), 4.18-3.77 (m, 4H), 2.36-2.28 (m, 1H), 0.99 (d, 6H); MS (EI) $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 2(d). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]formamide: ^{1}H NMR (400 MHz, DMSO): 8.69 (d, 1H), 8.58 (s, 1H), 8.02 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.19-7.13 (m, 1H), 6.70-6.66 (m, 1H), 4.55-4.46 (m, 1H), 4.42-4.36 (m, 1H), 4.20-4.16 (m, 1H), 4.01-3.97 (m, 1H), 3.82-3.79 (m, 1H); MS (EI) $C_{17}H_{13}F_3IN_3O_2$: 476 (MH^+).

EXAMPLE 2(e). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-3,4-dihydroxybutanamide: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 8.47 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.28 (m, 1H), 7.20-7.14 (m, 1H), 6.72-6.66 (m, 1H), 4.45-4.35 (m, 2H), 4.18-4.14 (m, 1H), 4.00-3.92 (m, 1H), 3.84-3.78 (m, 2H), 3.31-3.18 (m, 2H), 2.38-2.18 (m, 1H), 2.09-2.03 (m, 1H); MS (EI) $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 2(f). methyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate: ^{1}H NMR (400 MHz, DMSO): 8.58 (s, 1H), 7.84 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.35-7.27 (m, 1H), 7.20-7.13 (m, 1H), 6.71-6.66 (m, 1H), 4.38-4.25 (m, 2H), 4.17-4.12 (m, 1H), 4.00-3.97 (m, 1H), 3.83-3.78 (m, 1H), 3.53 (s, 3H); MS (EI) $C_{18}H_{15}F_3IN_3O_3$: 506 (MH^+).

EXAMPLE 2(g). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-(4-methylpiperazin-1-yl)acetamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.64 (s, 1H), 8.54 (d, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.32-7.29 (m, 1H), 7.21-7.15 (m, 1H), 6.72-6.66 (m, 1H), 4.54-4.28 (m, 2H), 4.19-4.15 (m, 1H), 4.06-4.00 (m, 1H), 3.91-3.84 (m, 1H), 3.44-3.24 (m, 2H), 3.16-2.92 (m, 6H), 2.78 (s, 3H), 2.62-2.50 (m, 2H); MS (EI) $C_{23}H_{25}F_3IN_5O_2$: 588 (MH^+).

EXAMPLE 2(h). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-bis(2-hydroxyethyl)glycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.19 (d, 1H), 7.60 (d, 1H), 7.41 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.51-4.40 (m, 2H), 4.23-4.18 (m, 1H), 4.05-3.98 (m, 3H), 3.86-3.82 (m, 1H), 3.75-3.69 (m, 3H), 3.32 (br s, 4H) $C_{22}H_{24}F_3IN_4O_4$: 593 (MH^+).

EXAMPLE 2(i). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-piperidin-1-ylacetamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.20 (d, 1H), 7.60 (d, 1H), 7.41 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.52-4.40 (m, 2H), 4.24-4.18 (m, 1H), 4.05-4.00 (m, 1H), 3.87-3.80 (m, 3H), 3.40-3.32 (m, 2H), 3.00-2.91 (m, 2H), 1.82-1.66 (m, 6H); MS (EI) $C_{23}H_{24}F_3IN_4O_2$: 573 (MH^+).

EXAMPLE 2(j). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N3-(2-hydroxyethyl)-N3-methyl-beta-alaninamide hydrochloride: ^{1}H NMR (400 MHz, DMSO): 9.36 (br s, 1H), 8.86 (d, 1H), 8.60 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.32-7.26 (m, 1H), 7.21-7.14 (m,

1H), 6.72-6.66 (m, 1H), 5.35-5.33 (m, 1H), 4.48-4.37 (m, 2H), 4.20-4.15 (m, 1H), 4.02-3.96 (m, 1H), 3.84-3.79 (m, 1H), 3.74-3.68 (m, 2H), 3.42-3.06 (m, 4H), 2.75 (s, 3H), 2.65-2.60 (m, 2H); MS (EI) $C_{22}H_{24}F_3IN_4O_3$: 577 (MH^+).

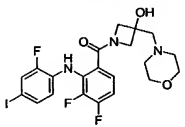
EXAMPLE 2(k). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N3,N3-bis(2-hydroxyethyl)-beta-alaninamide hydrochloride: ^{1}H NMR (400 MHz, DMSO): 9.39 (br s, 1H), 8.91 (d, 1H), 8.61 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.14 (m, 1H), 6.72-6.66 (m, 1H), 5.31 (br s, 2H), 4.46-4.36 (m, 2H), 4.20-4.15 (m, 1H), 4.02-3.97 (m, 1H), 3.85-3.72 (m, 5H), 3.30-3.17 (m, 4H), 2.68-2.63 (m, 2H); MS (EI) $C_{23}H_{26}F_3IN_4O_4$: 607 (MH^+).

EXAMPLE 2(m). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N2-methylglycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.09 (d, 1H), 8.69 (br s, 2H), 8.60 (s, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.22-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.54-4.41 (m, 2H), 4.25-4.19 (m, 1H), 3.99-3.96 (m, 1H), 3.84-3.78 (m, 1H), 3.72-3.67 (m, 2H), 2.58-2.54 (m, 3H); MS (EI) $C_{19}H_{18}F_3IN_4O_2$: 519 (MH^+).

EXAMPLE 2(n). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]glycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.59 (s, 1H), 8.46 (br s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.32-7.28 (m, 1H), 7.20-7.13 (m, 1H), 6.72-6.66 (m, 1H), 4.49 (br s, 1H), 4.40-4.35 (m, 1H), 4.18-4.13 (m, 1H), 4.05-4.01 (m, 1H), 3.86-3.81 (m, 1H), 3.07 (s, 2H); MS (EI) $C_{18}H_{16}F_3IN_4O_2$: 505 (MH^+).

EXAMPLE 3

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol



[00328] A mixture of 3-azetidinol hydrochloride (10 g, 91 mmol), di-*tert*-butyl dicarbonate (18.8 g, 86.3 mmol) and sodium bicarbonate (15.3 g, 182 mmol) in

dioxane:water (400 mL, 1:1) was stirred at room temperature for 15 hours. The organic portion was removed *in vacuo* and the aqueous portion was extracted with ethyl acetate three times. The combined organic portion was washed with 5% aqueous HCl, water, brine, dried over sodium sulfate, filtered and concentrated *in-vacuo* to afford 12.8 g, 74 mmol (81%) of 1,1-dimethylethyl 3-hydroxyazetidine-1-carboxylate as a colorless oil without further purification. ^{1}H NMR (400 MHz, DMSO): 5.62 (d, 1H), 4.40-4.33 (m, 1H), 4.02-3.95 (m, 2H), 3.62-3.54 (m, 2H), 1.37 (s, 9H). GC/MS for $C_8H_{15}NO_3$: 173.

[00329] A solution of oxalyl chloride (545 μL, 6.36 mmol) in dichloromethane (25 mL) was cooled to -78 °C. While maintaining an internal temperature of -78 °C, the dropwise addition of DMSO (903 μL, 12.7 mmol) followed by 1,1-dimethylethyl 3-hydroxyazetidine-1-carboxylate (1 g, 5.78 mmol in 30 mL of dichloromethane) and finally triethylamine (3.25 mL, 23.1 mmol in 20 mL of dichloromethane) was performed. The mixture was allowed to warm to room temperature and was stirred for 15 hours. The reaction mixture was diluted with water and partitioned and the organic portion was washed twice with water. The combined aqueous portion was extracted once with dichloromethane. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 893 mg, 5.20 mmol (90%) of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate as a colorless oil, which solidified upon standing. ^{1}H NMR (400 MHz, DMSO): 4.67 (s, 4H), 1.42 (s, 9H). GC/MS for $C_8H_{13}NO_3$: 171.

[00330] A mixture of potassium *tert*-butoxide (15.5 g, 137 mmol) and methyltriphenylphosphine bromide (49 g, 137 mmol) in diethyl ether (300 mL) was stirred at room temperature for 1 hour, followed by the addition of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (10 g, 58 mmol in 100 mL diethyl ether). The mixture was stirred at 35 °C for 2 hours and then allowed to cool to room temperature. The mixture was filtered through a pad of celite, washing with diethyl ether. The filtrate was partitioned with water and washed twice with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an orange oil which was purified by column chromatography. Eluting with 10% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 9.80 g, 58 mmol (100%) of 1,1-dimethylethyl

3-methylideneazetidine-1-carboxylate as a colorless oil. ^{1}H NMR (400 MHz, DMSO): 5.05-4.85 (m, 2H), 4.95-4.63 (m, 4H), 1.45 (s, 9H). GC-MS for $C_9H_{15}NO_2$: 169.

[00331] To a solution of 1,1-dimethylethyl 3-methylideneazetidine-1-carboxylate (2.96 g, 17.5 mmol) in chloroform (180 mL) was added 3-chloroperoxybenzoic acid (77%, 13.9 g, 62.0 mmol), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with a 1:1 mixture (150 mL) of 10% sodium thiosulfate and saturated sodium bicarbonate solutions. The organic portion was isolated, dried over sodium sulfate, filtered and concentrated to give an oily residue which was then purified by flash chromatography (15-50% ethyl acetate-hexanes) to give 1,1-dimethylethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (1.65g, 51%), GC-MS for $C_9H_{15}NO_3$: 185.

[00332] 1,1-Dimethylethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (51 mg, 0.28 mmol) was taken into THF (1 mL) followed by addition of morpholine (123 μL, 1.4 mmol) and the mixture was stirred for one hour at room temperature. The solution was then concentrated and the residue partitioned with ethyl acetate and water. The organic layer was washed once with water then brine and the organic layer dried over anhydrous sodium sulfate. Filtration and concentration gave a colorless oil that was purified by silica gel flash chromatography using ethyl acetate to 10% methanol in dichloromethane as eluents. The combined pure fractions were concentrated and the residue treated with neat TFA (1 mL) for 5 minutes then concentrated. The residue was taken into methanol (2 mL) and basified to pH > 10 by addition of Biorad AG-1X hydroxide form resin. Filtration and concentration afforded 3-(morpholin-4-ylmethyl)azetidin-3-ol (11.6 mg, 24% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): 3.69-3.66 (m, 4H), 3.55 (d, 2H), 3.49 (d, 2H), 2.66 (s, 2H), 2.57-2.55 (m, 4H).

[00333] 3-(Morpholin-4-ylmethyl)azetidin-3-ol (11.6 mg, 0.07 mmol) was taken into DMF (1 mL) followed by addition of DIPEA (35 μL, 0.21 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (28 mg, 0.07 mmol), prepared using procedures similar to those described in Reference 1, and the mixture was stirred for 30 minutes at room temperature. The solution was then concentrated *in vacuo* and the residue purified by preparative reverse phase HPLC. Lyophillization of the combined fractions gave 1-({3,4-difluoro-2-[(2-fluoro-4-

iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol trifluoroacetate salt (6.3 mg) as a colorless amorphous solid. ^{1}H NMR (400 MHz, CD_3OD): 7.48 (d, 1H), 7.36 (d, 1H), 7.33-7.29 (m, 1H), 7.08-7.02 (m, 1H), 6.65-6.60 (m, 1H), 4.39 (br d, 1H), 4.24-4.18 (br, 2H), 4.08-3.96 (br m, 3H), 3.80 (br s, 2H), 3.51 (d, 2H), 3.40 (br s, 2H), 3.24 (br s, 2H).

[00334] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds were prepared.

EXAMPLE 3(a). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(pyrrolidin-1-ylmethyl)azetidin-3-ol: MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 3(b). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}piperidin-4-ol: MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EXAMPLE 3(c). 3-{[bis(2-hydroxyethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EXAMPLE 3(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methylpiperazin-1-yl)methyl]azetidin-3-ol: MS (EI) for $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EXAMPLE 3(e). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methyl-1,4-diazepan-1-yl)methyl]azetidin-3-ol: MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(f). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[methyl(1-methylpyrrolidin-3-yl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(g). 3-(1,4'-bipiperidin-1'-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{27}H_{32}F_3IN_3O_2$: 629 (MH^+).

EXAMPLE 3(h). 3-({4-[2-(diethylamino)ethyl]piperazin-1-yl}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{27}H_{35}F_3IN_3O_2$: 647 (MH^+).

EXAMPLE 3(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-

hydroxyethyl)(methyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(j). 3-(azetidin-1-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(k). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 3(m). 3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{17}H_{15}F_3IN_3O_2$: 478 (MH^+).

EXAMPLE 3(n). *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}acetamide: MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 520 (MH^+).

EXAMPLE 3(o). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylethyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 534 (MH^+).

EXAMPLE 3(q). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(hydroxyamino)methyl]azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.32 (d, 1H), 4.05 (dd, 2H), 3.85 (d, 1H), 3.00 (s, 2H); MS (EI) for $C_{17}H_{15}F_3IN_3O_3$: 494 (MH^+).

EXAMPLE 3(r). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(methyloxy)amino]methyl}azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.35 (m, 1H), 7.27 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.26 (d, 1H), 4.08 (d, 1H), 4.00 (d, 1H), 3.84 (d, 1H), 3.30 (s, 3H), 3.00 (d, 2H); MS (EI) for $C_{18}H_{17}F_3IN_3O_3$: 508 (MH^+).

EXAMPLE 3(s). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(ethyloxy)amino]methyl}azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.34 (m, 1H), 7.26 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.26 (d, 1H), 4.12 (d, 1H), 4.00 (d, 1H), 3.84 (d, 1H), 3.61 (dd, 2H), 3.00 (s, 2H), 1.06 (t, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 3(t). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine

acetate salt: ^{1}H NMR (400 MHz, d_4-MeOH): 7.46 (2d, 1H), 7.36 (m, 1H), 7.30 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.18 (d, 1H), 4.08 (d, 1H), 4.02 (d, 1H), 3.88 (1*H*), 3.40 (s, 2H); MS (EI) for $C_{18}H_{17}F_3IN_5O_2$: 520 (MH^+).

EXAMPLE 3(u). *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}benzenecarboximidamide hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 7.70 (d, 3H), 7.58 (m, 2H), 7.46 (dd, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.28 (m, 1H), 4.15 (m, 2H), 3.96 (m, 1H), 3.78 (s, 2H); MS (EI) for $C_{24}H_{20}F_3IN_4O_2$: 581 (MH^+).

EXAMPLE 3(v). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyrimidin-2-ylamino)methyl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.48 (s, 2H), 7.46 (2d, 1H), 7.36 (m, 1H), 7.28 (m, 1H), 7.04 (m, 1H), 6.85 (t, 1H), 6.61 (m, 1H), 4.24 (d, 1H), 4.06 (t, 2H), 3.87 (d, 1H), 3.75 (d, 2H); MS (EI) for $C_{21}H_{17}F_3IN_5O_2$: 556 (MH^+).

EXAMPLE 3(w). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyridin-2-ylamino)methyl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 7.87 (dd, 1H), 7.85 (dd, 1H), 7.46 (2d, 1H), 7.36 (m, 2H), 7.06 (m, 2H), 6.89 (m, 1H), 6.61 (m, 1H), 4.53 (d, 2H), 4.46 (m, 1H), 4.28 (m, 1H), 4.16 (m, 1H), 3.96 (m, 1H); MS (EI) for $C_{22}H_{18}F_3IN_4O_2$: 555 (MH^+).

EXAMPLE 3(x). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(ethylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (s, 2H), 7.59 (d, 1H), 7.40 (d, 1H), 7.36-7.33 (m, 1H), 7.23-7.18 (m, 1H), 6.71 (s, 2H), 4.31-4.26 (m, 1H), 4.13-4.05 (m, 2H), 3.88-3.84 (m, 1H), 3.21 (br m, 2H), 2.97-2.90 (m, 2H), 1.19 (t, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 3(y). 3-[(cyclopropylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.99 (br s, 2H), 8.60 (s, 1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.36-7.33 (m, 1H), 7.23-7.16 (m, 1H), 6.72 (s, 2H), 4.34-4.29 (m, 1H), 4.14-4.04 (m, 2H), 3.88-3.84 (m, 1H), 2.70-2.64 (m, 1H), 0.89 (br s, 2H), 0.74-0.69 (br s, 2H). MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(z). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,2-trifluoroethyl)amino]methyl}azetidin-

3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (s, 1H), 7.58 (d, 1H), 7.38 (d, 1H), 7.35-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.72-6.67 (m, 1H), 4.25-4.19 (m, 1H), 4.07-3.98 (m, 2H), 3.86-3.77 (m, 2H), 3.19-3.09 (m, 2H). MS (EI) for $C_{19}H_{16}F_6IN_3O_2$: 560 (MH^+).

EXAMPLE 3(aa). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-1,2,3-triazol-1-ylmethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.55 (s, 1H), 8.04 (s, 1H), 7.66 (s, 1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.34-7.29 (m, 1H), 7.22-7.15 (m, 1H), 6.72-6.66 (m, 1H), 6.29 (s, 1H), 4.64 (s, 2H), 4.29-4.25 (m, 1H), 4.13-4.09 (m, 1H), 4.00-3.96 (m, 1H), 3.77-3.73 (m, 1H), 3.16 (d, 1H). MS (EI) for $C_{19}H_{15}F_3IN_5O_2$: 530 (MH^+).

EXAMPLE 3(bb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2-dimethylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (s, 1H), 8.30 (s, 2H), 7.59 (d, 1H), 7.39 (d, 1H), 7.36-7.17 (m, 4H), 6.77-6.66 (m, 4H), 4.35-4.30 (m, 1H), 4.16-4.08 (m, 2H), 3.92-3.87 (m, 1H), 3.31-3.27 (m, 2H), 2.78-2.74 (m, 2H), 1.76 (s, 4H), 0.99 (s, 9H). MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(cc). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(4-methylphenyl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.39 (dd, 1H), 7.31-7.34 (m, 1H), 7.08 (dd, 5H), 6.77-6.83 (m, 1H), 6.58-6.63 (m, 1H), 4.20 (br s, 1H), 4.01 (d, 1H), 2.87 (t, 4H), 2.75 (t, 4H), 2.5 (br s, 2H), 2.33 (s, 3H), 2.08 (s, 2H). MS (EI) for $C_{26}H_{25}F_3IN_3O_2$: 594 (M-H).

EXAMPLE 3(dd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.40 (dd, 1H), 7.32-7.34 (m, 1H), 7.15-7.22 (m, 4H), 7.10-7.14 (m, 1H), 6.77-6.83 (m, 1H), 6.58-6.64 (m, 1H), 4.22 (br s, 1H), 4.04 (d, 1H), 3.57-3.63 (m, 1H), 3.17 (dd, 2H), 2.94 (s, 2H), 2.75 (dd, 2H), 2.48 (br s, 4H), 2.08 (s, 2H). MS (EI) for $C_{26}H_{23}F_3IN_3O_2$: 592 (M-H).

EXAMPLE 3(ee). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1S,2S)-2-hydroxycyclopentyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.33-7.37 (m, 1H), 7.26-7.31 (m, 1H), 7.00-7.08 (m, 1H), 6.58-6.65 (m, 1H), 4.2 (t, 1H), 3.86-4.06 (m, 4H), 2.92-3.10 (m, 3H), 2.00-2.10 (m,

1H), 1.91-1.97 (m, 3H), 1.66-1.78 (m, 2H), 1.52-1.61 (m, 1H), 1.32-1.44 (m, 1H). MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 560 (M-H).

EXAMPLE 3(ff). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,2-dimethylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.33-7.37 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.08 (m, 1H), 6.59-6.64 (m, 1H), 4.14-4.22 (m, 1H), 3.98-4.06 (m, 2H), 3.84-3.90 (m, 1H), 2.86-3.20 (m, 2H), 2.65 (br s, 1H), 1.92 (s, 2H), 1.76-1.86 (m, 1H), 1.06 (d, 3H), 0.91 (dd, 6H). MS (EI) for $C_{22}H_{25}F_3I\,N_3O_2$: 546 (M-H).

EXAMPLE 3(gg). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-methyl-2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.55 (dd, 1H), 7.33-7.36 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.09 (m, 1H), 6.59-6.65 (m, 1H), 4.14-4.22 (m, 1H), 3.96-4.06 (m, 2H), 3.85-3.92 (m, 1H), 3.40-3.48 (m, 1H), 3.34 (s, 3H), 2.90-3.15 (m, 3H), 1.94 (s, 3H), 1.11 (d, 3H). MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 548 (M-H).

EXAMPLE 3(hh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.33-7.36 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.09 (m, 1H), 6.58-6.65 (m, 1H), 4.15-4.20 (m, 1H), 3.99-4.06 (m, 2H), 3.86-3.91 (m, 1H), 2.94 (s, 2H), 2.55-2.63 (m, 1H), 1.92 (s, 2H), 1.48-1.58 (m, 4H), 0.92 (t, 6H). MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 546 (M-H).

EXAMPLE 3(ii). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-1-ylmethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.67 (br s, 1H), 7.48 (m, 1H), 7.36 (m, 1H), 6.91 (br s, 1H), 6.63 (m, 1H), 4.25 (s, 2H), 4.22 (m, 1H), 4.02 (m, 2H), 3.82 (m, 1H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 3(jj). 3-{[(cyclopropylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.47 (m, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.05 (m, 1H), 6.62 (m, 1H), 4.30 (m, 1H), 4.24 (m, 2H), 3.99 (m, 1H), 3.66 (m, 2H), 2.91 (d, 2H), 1.08 (m, 1H), 0.71 (m, 2H), 0.40 (m, 2H). MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 3(kk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(phenylmethyl)amino]methyl}azetidin-3-ol

hydrochloride: ^{1}H NMR (400 MHz, CD_3OD): 7.47 (m, 5H), 7.43 (m, 1H), 7.35 (m, 1H), 7.27 (m, 1H), 7.04 (m, 1H), 6.61 (m, 1H), 4.24 (m, 3H), 4.08 (m, 2H), 3.96 (m, 1H). MS (EI) for $C_{24}H_{21}F_3IN_3O_2$: 568 (MH^+).

EXAMPLE 3(mm). 3-[(butylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.67 (dt, 1H), 4.04 (d, 1H), 3.88 (q, 2H), 3.69 (d, 1H), 2.59 (s, 2H), 1.90 (s, 2H), 1.22-1.33 (m, 4H), 0.84 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(nn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-ethylpyrrolidin-2-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.02 (t, 1H), 3.89 (q, 2H), 3.69 (d, 1H), 2.98 (s, 1H), 2.67-2.76 (m, 1H), 2.62 (s, 1H), 2.39-2.45 (m, 1H), 2.29 (s, 1H), 1.97-2.13 (m, 2H), 1.69 (s, 1H), 1.54 (s, 3H), 0.97 (t, 3H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(oo). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.32 (t, 1H), 7.18 (q, 1H), 6.68 (dt, 1H), 4.06 (d, 1H), 3.87 (d, 2H), 3.70 (d, 1H), 3.42 (t, 2H), 2.65 (s, 2H), 2.56 (dt, 2H). 1.91 (s, 2H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 3(pp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.02 (d, 1H), 3.87 (t, 2H), 3.70 (d, 1H), 2.62 (s, 1H), 2.54 (t, 1H), 2.23 (t, 1H), 2.09 (s, 4H), 7.85 (s, 6H); MS (EI) for $C_{21}H_{24}F_3IN_4O_2$: 549 (MH^+).

EXAMPLE 3(qq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dt, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.04 (d, 1H), 3.89 (d, 2H), 3.79 (d, 1H), 2.88-2.92 (m, 1H), 2.61 (s, 2H), 2.15 (s, 3H), 1.93-2.04 (m, 2H), 1.75-1.83 (m, 3H), 1.54-1.70 (m, 3H), 1.20-1.37 (m, 2H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(rr). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydrofuran-2-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.14 (q, 1H), 6.68 (dt, 1H), 5.75 (s, 1H), 4.03 (t, 1H), 3.87 (t, 2H), 3.76 (q, 1H), 3.68 (q, 2H), 3.54-3.58 (m, 1H), 2.63 (s, 2H), 1.91 (s, 2H), 1.71-1.87 (m, 3H), 1.40-1.48 (m, 1H); MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EXAMPLE 3(ss). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-pyrrolidin-1-ylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.04 (d, 1H), 3.89 (d, 2H), 3.69 (d, 1H), 2.60 (s, 1H), 2.34-2.37 (m, 4H), 1.86 (s, 8H), 1.64 (s, 2H), 1.46-1.53 (m, 1H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(tt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.86 (d, 2H), 3.70 (d, 1H), 3.21 (s, 3H), 2.63 (s, 4H), 1.88 (s, 2H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(uu). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methylpiperidin-4-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (t, 1H), 4.03 (d, 1H), 3.89 (t, 2H), 3.69 (d, 1H), 2.68 (d, 2H), 2.57 (s, 1H), 2.34 (d, 2H), 1.88 (s, 4H), 1.73 (t, 2H), 1.57 (d, 2H), 1.23 (s, 1H), 1.05 (q, 2H); MS (EI) for $C_{24}H_{28}F_3IN_4O_3$: 589 (MH^+).

EXAMPLE 3(vv). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(dimethylamino)butyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.18 (q, 1H), 6.68 (dt, 1H), 4.03 (t, 2H), 3.88 (t, 2H), 3.70 (d, 1H), 3.08 (s, 1H), 2.60 (s, 1H), 2.44-2.47 (m, 2H), 2.28-2.33 (m, 1H), 2.07-2.16 (m, 6H), 1.29-1.35 (m, 4H); MS (EI) for $C_{23}H_{28}F_3IN_4O_2$: 577 (MH^+).

EXAMPLE 3(ww). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-furan-2-ylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.49 (s, 1H), 7.36 (d,

1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (t, 1H), 6.33 (s, 1H), 6.08 (s, 1H), 5.72 (s, 1H), 4.04 (d, 1H), 3.87 (d, 2H), 3.70 (d, 1H), 2.74 (d, 2H), 2.69 (d, 2H), 2.64 (s, 2H); MS (EI) for $C_{23}H_{21}F_3IN_3O_3$: 572 (MH^+).

EXAMPLE 3(xx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-ethylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.56 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.67 (dt, 1H), 4.03 (d, 1H), 3.90 (d, 2H), 3.69 (d, 1H), 2.58 (s, 2H), 2.37 (d, 2H), 1.17-1.27 (m, 5H), 0.78 (t, 6H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 3(yy). 1,1-dimethylethyl [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propyl]carbamate: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.30-7.38 (m, 3H), 7.17 (q, 1H), 6.82 (t, 1H), 6.68 (dt, 1H), 4.07 (d, 1H), 3.89 (d, 2H), 3.70 (d, 1H), 3.36 (s, 2H), 2.93 (q, 2H), 2.61 (s, 2H), 1.46 (t, 2H), 1.36 (s, 9H); MS (EI) for $C_{25}H_{30}F_3IN_4O_4$: 635 (MH^+).

EXAMPLE 3(zz). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(pyrrolidin-2-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.53 (s, 1H), 7.58 (dd, 1H), 7.37 (d, 1H), 7.33 (d, 1H), 7.18 (q, 1H), 6.67 (dt, 1H), 6.25 (s, 1H), 4.07 (d, 1H), 3.96 (q, 2H), 3.78 (s, 3H), 3.34 (s, 6H), 1.73 (s, 1H), 1.35-1.39 (m, 1H); MS (EI) for $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EXAMPLE 3(aaa). 1,1-dimethylethyl 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)methyl]piperidine-1-carboxylate: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s, 1H), 7.56 (dd, 1H), 7.36 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.88 (t, 4H), 3.69 (d, 1H), 2.58 (s, 2H), 2.35 (d, 2H), 1.60 (d, 2H), 1.47 (s, 1H), 1.39 (s, 10H), 0.90 (q, 2H); MS (EI) for $C_{28}H_{34}F_3IN_4O_4$: 675 (MH^+).

EXAMPLE 3(bbb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s, 1H), 7.54 (dd, 1H), 7.35 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 7.05 (t, 2H), 6.64-6.72 (m, 3H), 4.07 (d, 1H), 3.90 (t, 2H), 3.78 (s, 2H), 3.72 (d, 1H), 2.65 (s, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ccc). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(3-

hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.56 (d, 1H), 7.35 (d, 1H), 7.29 (t, 1H), 7.16 (q, 1H), 7.06 (t, 1H), 6.64-6.72 (m, 3H), 6.60 (dd, 1H), 4.07 (d, 1H), 3.88 (t, 2H), 3.69 (d, 1H), 3.60 (s, 2H), 2.58 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ddd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(4-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.55 (dd, 1H), 7.35 (d, 1H), 7.27 (t, 1H), 7.16 (q, 1H), 7.06 (d, 2H), 6.64-6.70 (m, 3H), 4.04 (d, 1H), 3.85 (t, 2H), 3.68 (d, 1H), 3.55 (s, 2H), 2.56 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(eee). 3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-5-(hydroxymethyl)cyclopentane-1,2-diol: ^{1}H NMR (400MHz, d_6-DMSO): 8.60 (broad s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.32 (t, 1H), 7.16 (q, 1H), 6.68 (t, 1H), 4.06 (q, 2H), 3.86 (t, 3H), 3.72 (dd, 1H), 3.60 (t, 1H), 3.36-3.43 (m, 2H), 3.30 (dd, 1H), 2.80 (q, 1H), 2.62-2.72 (m, 2H), 1.88-1.95 (m, 1H), 0.82-0.90 (m, 1H); MS (EI) for $C_{23}H_{25}F_3IN_3O_5$: 608 (MH^+).

EXAMPLE 3(fff). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(piperidin-4-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (broad s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.87 (d, 2H), 3.69 (d, 1H), 3.01 (d, 2H), 2.59 (s, 2H), 2.43-2.56 (m, 1H), 2.35 (d, 2H), 1.65 (d, 2H), 1.47 (s, 1H), 1.07 (q, 2H); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(ggg). 3-{[(3-aminopropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H),, 6.68 (dt, 1H), 4.05 (d, 1H), 3.88 (d, 2H), 3.69 (d, 1H), 2.61 (t, 3H), 2.53-2.56 (m, 1H), 1.49 (t, 1.49); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 535 (MH^+).

EXAMPLE 3(hhh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({[2-(4-methylpiperazin-1-yl)phenyl]methyl}amino)methyl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (broad s, 1H), 7.55 (dd, 1H), 7.34 (t, 2H), 7.28 (d, 1H), 7.13-7.20 (m, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.66 (dt, 1H), 4.03 (d, 1H), 3.90 (t, 2H), 3.71 (d, 3H), 2.83 (s, 5H), 2.60 (s, 2H), 2.42 (s, 3H), 2.20 (s, 3H); MS (EI) for $C_{29}H_{31}F_3IN_5O_2$: 666 (MH^+).

EXAMPLE 3(iii). 3-[(1*H*-benzimidazol-2-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.04 (s, 2H), 7.28-7.35 (m, 2H), 7.23-7.26 (m, 2H), 7.09-7.12 (m, 2H), 6.80 (q, 1H), 6.57-6.63 (m, 1H), 5.28 (broad s, 2H), 4.38 (s, 3H), 4.25 (s, 1H), 4.21 (d, 2H); MS (EI) for $C_{24}H_{19}F_3IN_5O_2$: 594 (MH^+).

EXAMPLE 3(jjj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-imidazol-2-ylamino)methyl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 12.12 (s, 1H), 8.68 (s, 1H), 7.57-7.61 (m, 3H), 7.36-7.41 (m, 2H), 7.19 (q, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 6.71 (dt, 1H), 6.45 (s, 1H), 4.28 (d, 1H), 4.06 (d, 1H), 4.03 (d, 1H), 3.82 (d, 2H); MS (EI) for $C_{24}H_{17}F_3IN_5O_2$: 544 (MH^+).

EXAMPLE 3(kkk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(2,2,3,3,3-pentafluoropropyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (br s, 1H), 7.56 (dd, 1H), 7.37 (dd, 1H), 7.34-7.28 (m, 1H), 7.22-7.13 (m, 1H), 6.68 (ddd, 1H), 5.82 (br s, 1H), 4.06 (d, 1H), 3.91 (t, 2H), 3.70 (d, 1H), 3.40-3.25 (m, 2H), 2.76 (d, 2H), 2.40-2.31 (m, 1H); MS (EI) for $C_{20}H_{16}F_8IN_3O_2$: 610 (MH^+).

EXAMPLE 3(mmm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(3,3,3-trifluoropropyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (br s, 1H), 7.57 (dd, 1H), 7.37 (dd, 1H), 7.34-7.28 (m, 1H), 7.22-7.13 (m, 1H), 6.68 (ddd, 1H), 5.76 (br s, 1H), 4.05 (d, 1H), 3.88 (d, 2H), 3.70 (d, 1H), 2.71 (t, 2H), 2.63 (s, 2H), 2.41-2.26 (m, 2H); MS (EI) for $C_{20}H_{18}F_6IN_3O_2$: 574 (MH^+).

EXAMPLE 3(nnn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-1-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.61-8.56 (m, 1H), 7.55 (d, 1H), 7.37-7.07 (m, 8H), 6.71-6.64 (m, 1H), 4.16-4.05 (m, 2H), 3.98-3.85 (m, 2H), 3.72-3.68 (m, 1H), 2.90-2.82 (m, 1H), 2.74-2.64 (m, 2H), 1.91 (s, 3H), 1.73-1.63 (m, 1H); MS (EI) for $C_{26}H_{23}F_3IN_3O_2$: 594 (MH^+).

EXAMPLE 3(ooo). 3-[(cyclooctylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.55 (d, 1H), 7.20-7.14 (m, 2H), 6.70-6.66 (m, 1H), 4.03-3.98 (m, 1H), 3.92-3.86 (m, 2H), 3.72-3.67 (m, 1H), 2.60 (s, 2H), 1.90 (s, 3H), 1.64-1.22 (m, 15H); MS (EI) for $C_{25}H_{29}F_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(ppp). 3-[(cycloheptylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.55 (s, 1H), 7.55 (d, 1H), 7.36-7.28 (m, 2H), 7.21-7.14 (m, 1H), 6.70-6.66 (m, 1H), 4.04-4.00 (m, 1H), 3.92-3.85 (m, 2H), 3.71-3.66 (m, 1H), 2.60 (s, 2H), 1.90 (s, 3H), 1.70-1.13 (m, 13H); MS (EI) for $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EXAMPLE 3(qqq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-3-ylethyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.58 (s, 1H), 8.42-8.37 (m, 2H), 7.62-7.54 (m, 2H), 7.38-7.27 (m, 3H), 7.21-7.14 (m, 1H), 6.71-6.66 (m, 1H), 4.06-4.02 (m, 1H), 3.90-3.86 (m, 2H), 3.72-3.68 (m, 1H), 2.80-2.64 (m, 6H), 1.90 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EXAMPLE 3(rrr). *N*-cyclohexyl-N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-2-methylalaninamide acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.66 (br s 1H), 8.55 (s, 1H), 7.93-7.90 (m, 1H), 7.58 (d, 1H), 7.40-7.31 (m, 2H), 7.24-7.17 (m, 1H), 6.71-6.66 (m, 1H), 6.60 (br s, 1H), 4.28-4.23 (m, 1H), 4.14-4.02 (m, 2H), 3.89-3.83 (m, 1H), 3.12 (br s, 2H), 1.90 (s, 3H), 1.74-1.42 (m, 11H), 1.31-1.02 (m, 6H); MS (EI) for $C_{27}H_{32}F_3IN_4O_3$: 645 (MH^+).

EXAMPLE 3(sss). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.56 (d, 1H), 7.38-7.27 (m, 2H), 7.20-7.14 (m, 1H), 6.71-6.66 (m, 1H), 4.05-4.01 (m, 1H), 3.91-3.78 (m, 4H), 3.71-3.67 (m, 1H), 3.25-3.18 (m, 2H), 2.60 (s, 2H), 2.36 (d, 2H), 1.90 (s, 3H), 1.57-1.50 (m, 3H), 1.13-1.02 (m, 2H); MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(ttt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)-1-methylethyl]amino}methyl)azetidin-3-ol trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.59-8.54 (m, 1H), 7.56 (d, 1H), 7.38-7.28 (m, 2H), 7.21-7.13 (m, 1H), 6.71-6.63 (m, 1H), 4.04-3.95 (m, 1H), 3.88-3.78 (m, 2H), 3.73-3.68 (m, 1H), 2.70-2.50 (m, 3H), 2.08 (s, 6H), 1.88 (s, 2H), 0.85-0.82 (m, 3H); MS (EI) for $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EXAMPLE 3(uuu). *N*-cyclopropyl-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-

yl]methyl}amino)cyclopentanecarboxamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.80 (br s, 1H), 8.58 (s, 1H), 8.04 (s, 1H), 7.59 (d, 1H), 7.40-7.31 (m, 2H), 7.25-7.16 (m, 1H), 6.74-6.58 (m, 2H), 4.26-3.82 (m, 4H), 3.10 (br s, 2H), 2.69-2.64 (m, 1H), 2.11-1.88 (m, 4H), 1.82-1.61 (m, 4H), 0.67-0.62 (m, 2H), 0.52-0.48 (m, 2H); MS (EI) for $C_{26}H_{28}F_3IN_4O_3$: 629 (MH^+).

EXAMPLE 3(vvv). N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-*N*-ethyl-2-methylalaninamide acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 7.60-7.72 (m, 1H), 7.56 (d, 1H), 7.38-7.30 (m, 2H), 7.22-7.14 (m, 1H), 6.69-6.63 (m, 1H), 4.07-4.04 (m, 1H), 3.95-3.90 (m, 2H), 3.72-3.68 (m, 1H), 3.05-3.01 (m, 2H), 2.47 (br s, 2H), 1.90 (s, 3H), 1.09 (s, 6H), 0.94 (t, 3H); MS (EI) for $C_{23}H_{26}F_3IN_4O_3$: 591 (MH^+).

EXAMPLE 3(www). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2-methylhydrazino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.54 (s, 1H), 7.57 (d, 1H), 7.38-7.30 (m, 2H), 7.19-7.12 (m, 1H), 6.69-6.63 (m, 1H), 4.04-4.01 (m, 1H), 3.92-3.84 (m, 2H), 3.68-3.63 (m, 1H), 2.55 (s, 2H), 2.39 (s, 3H), 1.90 (s, 3H); MS (EI) for $C_{18}H_{18}F_3IN_4O_2$: 507 (MH^+).

EXAMPLE 3(xxx). 3-[(azetidin-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 7.57 (d, 1H), 7.39-7.30 (m, 2H), 7.20-7.13 (m, 1H), 6.70-6.65 (m, 1H), 4.10-4.04 (m, 1H), 3.90-3.83 (m, 2H), 3.78-3.67 (m, 3H), 3.61-3.53 (m, 1H), 3.48-3.42 (m, 2H), 2.61-2.54 (m, 2H), 1.90 (s, 3H); MS (EI) for $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EXAMPLE 3(yyy). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3-thiazol-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 7.57 (d, 1H), 7.38-7.28 (m, 2H), 7.20-7.13 (m, 1H), 6.75 (d, 1H), 6.70-6.64 (m, 1H), 5.93 (d, 1H), 4.26-4.22 (m, 1H), 4.11-4.08 (m, 1H), 4.00-3.88 (m, 3H), 3.74-3.70 (m, 1H), 1.90 (s, 3H); MS (EI) for $C_{20}H_{16}F_3IN_4O_2S$: 561 (MH^+).

EXAMPLE 3(zzz). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methyloxy)phenyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8.57 (s, 1H), 7.56 (d, 1H), 7.38-7.30 (m, 2H), 7.20-7.12 (m, 1H), 6.95-6.91 (m, 1H), 6.70-6.66 (m, 1H), 6.21-6.17 (m, 2H), 6.14-6.10 (m, 1H), 5.94 (s, 1H), 5.49-5.44 (m, 1H),

4.14-4.10 (m, 1H), 3.98-3.93 (m, 2H), 3.78-3.75 (m, 1H), 3.65 (s, 3H), 3.21 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ab). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(methyloxy)phenyl]amino}methyl)azetidin-3-ol: ^1H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.58 (d, 1H), 7.39-7.30 (d, 2H), 7.20-7.13 (m, 1H), 6.71-6.66 (m, 3H), 6.55 (d, 2H), 5.93 (s, 1H), 5.00-4.95 (m, 1H), 4.14-4.08 (m, 1H), 3.98-3.92 (m, 2H), 3.79-3.74 (m, 1H), 3.63 (s, 3H), 3.13 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ac). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(ethyloxy)ethyl]amino}methyl)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.24-4.16 (d, 1H), 4.08-3.98 (t, 2H), 3.92-3.85 (d, 1H), 3.60-3.55 (t, 2H), 3.54-3.47 (q, 2H), 3.01-2.96 (s, 2H), 2.94-2.89 (t, 2H), 1.20-1.15 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(ad). 3-({[2,2-bis(methyloxy)ethyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.32 (d, 1H), 7.30-7.24 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.57 (t, 1H), 4.48-4.42 (t, 1H), 4.20-4.11 (d, 1H), 4.02-3.93 (t, 2H), 3.86-3.80 (d, 1H), 3.38-3.34 (s, 6H), 2.84-2.80 (s, 2H), 2.75-2.70 (d, 2H),1.93-1.87 (s, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EXAMPLE 3(ae). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxypropyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.31-4.23 (d, 1H), 4.16-4.05 (t, 2H), 3.99-3.89 (d, 1H), 3.70-3.64 (t, 2H), 3.26-3.22 (s, 2H), 3.11-3.04 (t, 2H), 1.93-1.89 (s, 3H), 1.89-1.82 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(af). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-4-ylethyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 8.36-8.32 (d, 2H), 7.38-7.33 (d, 1H), 7.26-7.14 (m, 3H), 7.00-6.91 (q, 1H), 4.12-4.04 (d, 1H), 3.96-3.88 (t, 2H), 3.80-3.73 (d, 2H), 2.92-2.74 (m, 6H), 1.87-1.84 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EXAMPLE 3(ag). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)pyrrolidin-3-

yl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.47-7.24 (m, 8H), 7.08-7.00 (q, 1H), 6.64-6.57 (t, 1H), 4.19-4.11 (d, 1H), 4.05-3.81 (m, 5H), 3.52-3.44 (m, 1H), 3.09-2.99 (m, 2H), 2.91-2.76 (m, 3H), 1.93-1.91 (s, 3H), 1.82-1.71 (m, 1H); MS (EI) for $C_{28}H_{28}F_3IN_4O_2$: 637 (MH^+).

EXAMPLE 3(ah). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2-thienyl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.47-7.42 (d, 1H), 7.36-7.31 (d, 1H), 7.30-7.24 (m, 1H), 7.21-7.17 (d, 1H), 7.08-7.00 (q, 1H), 6.93-6.89 (t, 1H), 6.86-6.83 (d, 1H), 6.64-6.57 (t, 1H), 4.18-4.11 (d, 1H), 4.01-3.93 (t, 2H), 3.85-3.78 (d, 1H), 3.04-2.97 (t, 2H), 2.92-2.87 (t, 2H), 2.82-2.78 (s, 2H), 1.92-1.87 (s, 3H); MS (EI) for $C_{23}H_{21}F_3IN_3O_2S$: 588 (MH^+).

EXAMPLE 3(ai). 3-[({2-[bis(1-methylethyl)amino]ethyl}amino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.18-4.13 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 2H), 3.57-3.47 (q, 2H), 3.05-2.99 (t, 2H), 2.92-2.85 (t, 4H), 1.92-1.88 (s, 3H), 1.28-1.22 (d, 12H); MS (EI) for $C_{25}H_{32}F_3IN_4O_2$: 605 (MH^+).

EXAMPLE 3(aj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(phenyloxy)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.36-7.31 (d, 1H), 7.26-7.22 (d, 1H), 7.20-7.13 (m, 3H), 6.97-6.89 (t, 1H), 6.86-6.80 (m, 3H), 6.54-6.47 (t, 1H), 4.13-4.07 (d, 1H), 4.01-3.96 (t, 2H), 3.79-3.74 (d, 1H), 2.97-2.91 (t, 2H), 2.84-2.79 (s, 2H), 1.84-1.81 (s, 3H); MS (EI) for $C_{25}H_{23}F_3IN_3O_3$: 598 (MH^+).

EXAMPLE 3(ak). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxypropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.27-4.19 (d, 1H), 4.10-4.00 (m, 2H), 3.15-3.00 (t, 2H), 3.57-3.47 (q, 2H), 3.15-3.00 (t, 2H), 2.87-2.81 (d, 1H), 2.72-2.64 (t, 1H), 1.94-1.91 (s, 3H), 1.19-1.15 (d, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(am). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(1-methylethyl)oxy]ethyl}amino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz,

CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.21-4.13 (d, 1H), 4.04-3.95 (t, 2H), 3.88-3.82 (d, 1H), 3.64-3.51 (m, 3H), 2.89-2.84 (s, 2H), 2.83-2.77 (t, 2H), 1.91-1.89 (s, 3H), 1.15-1.12 (d, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O_3$: 564 (MH^+).

EXAMPLE 3(an). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpiperidin-3-yl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.17-4.10 (d, 1H), 4.04-3.95 (t, 2H), 3.88-3.82 (d, 1H), 3.24-3.06 (m, 2H), 2.95-2.75 (m, 6H), 2.76-2.46 (m, 2H), 1.93-1.90 (s, 3H), 1.74-1.62 (m, 1H), 1.44-1.31 (m, 1H), 1.28-1.20 (t, 3H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(ao). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}methyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.20-4.13 (d, 1H), 4.00-3.90 (t, 2H), 3.83-3.75 (d, 1H), 2.84-2.78 (s, 2H), 2.53-2.48 (s, 2H), 1.93-1.87 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_3$: 574 (MH^+).

EXAMPLE 3(ap). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylbutyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.27 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.12-4.02 (t, 2H), 3.96-3.90 (d, 1H), 3.16-2.96 (m, 3H), 1.91-1.89 (s, 3H), 1.68-1.57 (m, 1H), 1.49-1.29 (m, 3H), 1.23-1.18 (d, 3H), 0.99-0.92 (t, 3H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(aq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.27-4.20 (d, 1H), 4.14-4.03 (t, 2H), 3.98-3.92 (d, 1H), 3.20-3.16 (s, 2H), 3.07-2.97 (m, 1H), 1.91-1.89 (s, 3H), 1.80-1.70 (m, 1H), 1.54-1.41 (m, 1H), 1.26-1.22 (d, 3H), 1.00-0.94 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(ar). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylbutyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H),

7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.26-4.19 (d, 1H), 4.10-4.01 (t, 2H), 3.94-3.87 (d, 1H), 3.05-2.99 (s, 2H), 2.77-2.70 (m, 1H), 2.61-2.54 (m, 1H), 1.91-1.89 (s, 3H), 1.73-1.61 (m, 1H), 1.49-1.39 (m, 1H), 1.24-1.12 (m, 1H), 0.94-0.84 (m, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O2$: 548 (MH^+).

EXAMPLE 3(as). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pentylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.29-4.23 (d, 1H), 4.15-4.05 (t, 2H), 3.98-3.90 (d, 1H), 3.21-3.18 (s, 2H), 2.93-2.86 (m, 2H), 1.91-1.89 (s, 3H), 1.70-1.60 (m, 2H), 1.42-1.29 (m, 4H), 0.97-0.90 (t, 3H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(at). 3-[(cyclohexylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.34 (d, 1H), 7.33-7.27 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.14-4.03 (t, 2H), 3.98-3.90 (d, 1H), 3.21-3.18 (s, 2H), 2.93-2.86 (m, 1H), 2.07-2.00 (d, 2H), 1.92-1.90 (s, 3H), 1.89-1.82 (d, 2H), 1.73-1.66 (d, 1H), 1.42-1.14 (m, 5H); MS (EI) for $C_{23}H_{25}F_3IN_3O_2$: 560 (MH^+).

EXAMPLE 3(au). 3-[(azepan-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.19-4.13 (d, 1H), 4.05-3.95 (t, 2H), 3.90-3.81 (d, 1H), 3.37-3.34 (s, 2H), 3.22-3.03 (m, 2H), 2.91-2.64 (m, 3H), 1.93-1.89 (s, 3H), 1.88-1.52 (m, 6H); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(av). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.58-7.54 (d, 1H), 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.14-6.99 (m, 4H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.10-4.02 (t, 2H), 3.95-3.88 (d, 1H), 3.23-3.03 (m, 9H), 1.94-1.92 (s, 3H); MS (EI) for $C_{27}H_{26}F_3IN_4O_2$: 623 (MH^+).

EXAMPLE 3(aw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3,5-triazin-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 8.48-8.46 (s, 1H), 8.36-8.34 (s, 1H), 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.28-7.22 (m, 1H), 7.06-6.98 (q, 1H), 6.65-6.58

(t, 1H), 4.24-4.18 (d, 1H), 4.10-3.96 (t, 2H), 3.84-3.78 (d, 1H), 3.69-3.67 (s, 2H), 1.99-1.97 (s, 3H); MS (EI) for $C_{20}H_{16}F_3IN_6O_2$: 557 (MH^+).

EXAMPLE 3(ax). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxycyclohexyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.22-4.15 (d, 1H), 4.08-3.99 (t, 2H), 3.93-3.87 (d, 1H), 3.56-3.47 (m, 1H), 3.05-3.02 (s, 2H), 2.76-2.68 (m, 1H), 2.03-1.96 (m, 4H), 1.93-1.89 (s, 3H), 1.35-1.23 (m, 4H); MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(ay). 3-[(cyclopent-3-en-1-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 5.70-5.65 (s, 2H), 4.20-4.14 (d, 1H), 4.03-3.95 (t, 2H), 3.90-3.81 (d, 1H), 3.58-3.50 (m, 1H), 2.90-2.86 (s, 2H), 2.68-2.58 (m, 2H), 2.26-2.16 (m, 2H), 1.93-1.89 (s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_3O_2$: 544 (MH^+).

EXAMPLE 3(az). *N*-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.27-7.20 (m, 3H), 7.09-7.01 (q, 1H), 6.65-6.55 (m, 3H), 4.22-4.16 (d, 1H), 4.08-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.28-3.24 (s, 2H), 2.08-2.05 (s, 3H), 2.91-2.64 (m, 3H), 1.93-1.89 (s, 3H); MS (EI) for $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EXAMPLE 3(ba). *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.27-7.20 (m, 1H), 7.04-6.96 (m, 3H), 6.72-6.68 (d, 1H), 6.65-6.58 (t, 1H), 6.40-6.35 (d, 1H), 4.24-4.18 (d, 1H), 4.08-3.98 (t, 2H), 3.87-3.81 (d, 1H), 3.28-3.25 (s, 2H), 2.10-2.07 (s, 3H), 1.97-1.95 (s, 3H); MS (EI) for $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EXAMPLE 3(bc). (1R,2S)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentane-1,2-diol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.58-8.54 (s, 1H), 7.61-7.53 (d, 1H), 7.39-7.28 (m, 2H), 7.21-7.13 (m, 1H), 6.71-6.63 (t, 1H), 5.58-5.64 (s, 1H), 5.63-5.58 (s, 1H), 4.06-4.01 (d, 1H), 3.90-3.84 (t, 2H),

3.72-3.66 (d, 1H), 3.31-3.26 (m, 3H), 2.61-2.57 (s, 2H), 2.46-2.36 (m, 2H), 2.02-1.93 (dd, 2H), 1.91-1.88 (s, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_4$: 578 (MH^+).

EXAMPLE 3(bd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclohexyl]amino}methyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.22-4.15 (d, 1H), 4.08-3.99 (t, 2H), 3.89-3.83 (d, 1H), 3.49-3.45 (s, 2H), 2.86-2.80 (s, 2H), 1.91-1.89 (s, 3H), 1.67-1.34 (m, 10H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EXAMPLE 3(be). 3-{[(3-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.08-6.98 (m, 2H), 6.65-6.55 (m, 3H), 6.53-6.44 (d, 1H), 4.22-4.15 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.27-3.24 (s, 2H), 1.91-1.89 (s, 3H); MS (EI) for $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(bf). 3-{[(4-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.45-7.40 (d, 1H), 7.35-7.30 (d, 1H), 7.28-7.22 (m, 1H), 7.06-6.97 (m, 3H), 6.62-6.54 (m, 3H), 6.53-6.44 (d, 1H), 4.22-4.15 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.26-3.22 (s, 2H), 1.96-1.94 (s, 3H); MS (EI) for $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(bg). 3-[(5-amino-3-methyl-1*H*-pyrazol-1-yl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.38-7.33 (d, 1H), 7.28-7.24 (d, 1H), 7.21-7.15 (m, 1H), 6.98-6.90 (q, 1H), 6.56-6.49 (t, 1H), 5.16-5.14 (s, 1H), 4.36-4.30 (d, 1H), 4.22-4.16 (d, 1H), 3.99-3.97 (s, 1H), 3.95-3.90 (d, 1H), 3.77-3.71 (d, 1H), 1.96-1.92 (s, 3H), 1.85-1.82 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EXAMPLE 3(bh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(5-methyl-1*H*-pyrazol-3-yl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.38-7.33 (d, 1H), 7.28-7.24 (d, 1H), 7.21-7.15 (m, 1H), 6.98-6.90 (q, 1H), 6.56-6.49 (t, 1H), 5.22-5.19 (s, 1H), 4.15-4.08 (d, 1H), 4.02-3.88 (m, 2H), 3.75-3.68 (d, 1H), 3.20-3.18 (s, 2H), 2.07-2.05 (s, 3H), 1.85-1.82 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EXAMPLE 3(bi). 3-[(diethylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (s, 1H), 7.58-7.55 (dd, 1H), 7.38-7.35 (dt, 1H), 7.33-7.31 (m, 1H), 7.22-7.15 (m, 1H), 6.69-6.64 (m, 1H), 5.56 (b, 1H), 4.06-4.04 (d, 1H), 3.90-3.88 (m, 2H), 3.72-3.69 (d 1H), 2.51-2.49 (m, 6H), 0.86-0.83 (t, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(bj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(dimethylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO):
8.56 (s, 1H), 7.59-7.56 (dd, 1H), 7.38-7.36 (dt, 1H), 7.34-7.33 (m, 1H), 7.21-7.14 (m, 1H), 6.71-6.65 (m, 1H), 5.55 (b, 1H), 4.07-4.05 (d, 1H), 3.89-3.84 (t, 2H), 3.74-3.719 (d, 1H), 2.46 (m, 2H), 2.19 (br s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 3(bk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.40 (s, 1H), 7.38 (dd, 1H), 7.33-7.30 (m, 1H), 7.12 (m, 1H), 6.85-6.79 (m, 1H), 6.63-6.57 (m, 1H), 4.22-4.11(br m, 4H), 3.55 (s, 2H), 3.15 (s, 2H), 1.32 (s, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(bm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(prop-2-en-1-ylamino)methyl]azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.47 (s, 1H), 7.40 (dd, 1H), 7.34-7.31 (m, 1H), 7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 6.64-6.59 (m, 1H), 5.88-5.78 (m, 1H), 5.00-5.12 (m, 2H), 4.13 (br m, 4H), 3.26 (d, 2H), 2.88 (d, 2H), 2.02 (s, 1H); MS (EI) for $C_{21}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(bn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(tetrahydro-2H-pyran-4-yl)ethyl]amino}methyl)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.45 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.26-4.04 (m, 4H), 3.95 (dd, 2H), 3.35 (t, 2H), 2.92 (d, 2H), 2.67 (m, 2H), 1.40-1.25 (m, 8H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EXAMPLE 3(bo). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylprop-2-yn-1-yl)amino]methyl}azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.64-6.58 (m, 1H),

4.20 (br, 1H), 4.07 (br, 1H), 2.92 (s, 2H), 1.58 (m, 4H), 0.92 (dd, 6h); MS (EI) for $C_{22}H_{21}F_3IN_3O_2$: 572 (MH^+).

EXAMPLE 3(bp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1*H*-imidazol-4-yl)ethyl]amino}methyl)azetidin-3-ol): ^1H NMR (400MHz, $CDCl_3$): 8.44 (s, 1H), 7.33-7.14 (m, 3H), 7.00 (m, 1H), 6.67 (dd, 1H), 6.59 (s, 1H), 6.44 (m, 1H), 3.93 (d, 2H), 2.75 (m, 2H), 2.60 (m, 1H), 2.42 (m, 1H) 2.02 (AcOH; s, 3H), 1.86 (m, 4H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(bq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(ethyloxy)propyl]amino}methyl)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.83-6.76 (m, 1H), 6.64-6.58 (m, 1H), 4.26-4.03 (br m, 4H), 3.53-3.44 (m, 4H), 2.92-2.73 (m, 4H), 1.72 (m, 2H) 1.18 (t, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 564 (MH^+).

EXAMPLE 3(br). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3-dimethylbutyl)amino]methyl}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.18 (br, 3H), 3.15 (s, 2H), 2.71 (m, 2H) 2.05 (AcOH; s, 3H), 1.43 (m, 2H), 0.90 (s, 9H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 3(bs). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-methylbutyl)amino]methyl}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.27-3.61 (br m, 6H), 2.98 (m, 2H), 2.72 (t, 2H) 2.05 (AcOH; s, 3H), 1.61 (m,1H), 1.43 (m, 2H), 0.90 (d, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 547 (MH^+).

EXAMPLE 3(bt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(dimethylamino)propyl]amino}methyl)azetidin-3-ol: MS (EI) for $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EXAMPLE 3(bu). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(1*H*-imidazol-1-yl)propyl]amino}methyl)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$):

8.46 (s, 1H), 7.53 (s, 1H), 7.40 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.09 (m, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.24-4.00 (br m, 6H), 2.84 (m, 2H), 2.61 (m, 2H), 1.94 (m, 2H); MS (EI) for $C_{23}H_{21}F_3IN_5O_2$: 586 (MH^+).

EXAMPLE 3(bv). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methylthio)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.26-4.03 (br m, 4H), 2.88 (s, 2H), 2.82 (t, 2H), 2.62 (t, 2H), 2.08 (s, 3H); MS (EI) for $C_{23}H_{21}F_3IN_3O_2S$: 552 (MH^+).

EXAMPLE 3(bw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1,3,3-tetramethylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.38 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 4.25-4.01 (br m, 4H), 2.82 (s, 2H), 1.45 (s, 2H), 1.15 (s, 6H), 0.90 (s, 9H); MS (EI) for $C_{25}H_{31}F_3IN_3O_2$: 590 (MH^+).

EXAMPLE 3(bx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.65-6.59 (m, 1H), 4.27-4.01 (br m, 4H), 2.82 (s, 2H), 1.46 (s, 2H), 1.08 (s, 6H), 0.89 (s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_4O_3$: 548 (MH^+).

EXAMPLE 3(by). 3-{[(3-amino-2-hydroxypropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{23}H_{22}F_3IN_4O_3$: 551 (MH^+).

EXAMPLE 3(bz). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}pyrrolidin-3-ol: MS (EI) for $C_{21}H_{21}F_3IN_3O_3$: 548 (MH^+).

EXAMPLE 3(ca). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({(2S)-2-[(methyloxy)methyl]pyrrolidin-1-yl}methyl)azetidin-3-ol: MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$):

8.46 (s, 1H), 7.41 (dd, 1H), 7.35-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.89-5.98 (m, 6H), 4.92 (s, 1H), 4.28-4.05 (br m, 4H), 3.44 (s, 2H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(cd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$):

8.46 (s, 1H), 7.78 (s, 1H), 7.40-7.05 (m, 4H), 6.72 (m, 1H), 6.62 (d, 1H), 6.50 (m, 1H), 6.42 (d, 1H) 4.04-3.98 (m, 4H), 3.18 (s, 2H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(ce). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$):

8.52 (s, 1H), 8.22 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.85 (dd, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 6.15 (d, 1H) 6.09-6.01 (m, 3H), 4.16-3.95 (br m, 4H), 3.22 (d, 2H) 2.15 (AcOH; s, 3H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(cf). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenyloxy)methyl]azetidin-3-ol: MS (EI) for $C_{23}H_{18}F_3IN_2O_3$: 555 (MH^+).

EXAMPLE 3(cg). 3-({[1-({3, 4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propane-1,2-diol: MS (EI) for $C_{20}H_{21}F_3IN_3O_4$: 552 (MH^+).

EXAMPLE 3(ch). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylthio)methyl]azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$):

8.46 (s, 1H), 7.45-7.23 (m, 5H), 7.14-7.05 (m, 1H), 6.78 (dd, 1H), 6.60 (m, 1H), 4.14-3.92 (br m, 4H), 3.33 (s, 2H); MS (EI) for $C_{23}H_{18}F_3IN_2O_2$: 571 (MH^+).

EXAMPLE 3(ci). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxybutyl)amino]methyl}azetidin-3-ol): ^1H NMR (400MHz, $CDCl_3$): 8.43 (s, 1H), 7.38 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.26-4.04 (m, 4H), 3.61 (m, 2H), 2.96 (s, 2H), 2.73 (s, 2H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(cj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)oxy]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.51 (s, 1H), 7.39 (dd, 1H), 7.35-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.21-4.05 (br m, 4H), 3.77 (m, 2H), 3.66 (m, 2H); MS (EI) for $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EXAMPLE 3(ck). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1S,2S)-2-hydroxycyclohexyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethyl-2-pyrrolidin-1-ylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.29 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 4.25-4.07 (br m, 4H), 2.88 (d, 2H), 2.62 (m, 4H), 2.58 (m, 2H), 1.78 (m, 4H), 2.05 (AcOH; s, 3H); MS (EI) for $C_{25}H_{30}F_3IN_4O_2$: 603 (MH^+).

EXAMPLE 3(cn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-4-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.41-7.11 (m, 3H), 7.12 (m, 1H), 6.85-6.79 (m, 2H), 4.12-3.98 (br m, 4H), 3.78 (s, 2H), 3.66 (s, 3H), 2.95 (s, 2H), 2.08 (AcOH; s, 4H) ,2.05 (AcOH; s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(co). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.45 (s, 1H), 7.47 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.91 (s, 1H), 6.87-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.18-4.02 (m, 4H), 3.3.80 (s, 2H), 3.62 (s, 3H), 2.90 (s, 1H), 2.05 (AcOH; s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(cp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2S)-2-(methyloxy)cyclopentyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1R)-2-

hydroxycyclohexyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cr). *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]methanesulfonamide: ^{1}H NMR (400MHz, $CDCl_3$): 7.33 (dd, 1H), 7.22 (m, 1H), 7.08 (dd, 1H), 6.83-6.77 (m, 1H), 6.03-5.98 (m, 2H), 6.64-6.59 (m, 1H), 4.08-3.77 (br m, 5H), 2.88 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_4S$: 647 (MH^+).

EXAMPLE 3(cs). 3-{[(4-aminophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.44 (s, 1H), 7.39 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.64-6.53 (m, 5H), 4.22-4.04 (br m, 4H), 3.34 (s, 2H); MS (EI) for $C_{23}H_{20}F_3IN_4O_2$: 569 (MH^+).

EXAMPLE 3(ct). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-2-methylcyclopentyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cu). 3-[(cyclopentylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.44 (dd, 1H), 7.36-7.31 (m, 1H), 7.30-7.24 (m, 1H), 7.09-6.99 (m, 1H), 6.64-6.57 (m, 1H), 4.17-4.10 (m,1H), 4.01-3.91 (m, 2H), 3.87-3.79 (m, 1H), 3.07-2.97 (m, 1H), 2.75 (s, 2H), 1.92-1.79 (m, 2H), 1.75-1.62 (m, 2H), 1.61-1.47 (m, 2H), 1.37-1.22 (m, 2H). MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+)

EXAMPLE 3(cv). 3-{[(cyclohexylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.39-7.32 (m, 1H), 7.31-7.25 (m, 1H), 7.11-6.99 (m, 1H), 6.67-6.57 (m, 1H), 4.27-4.15 (m, 1H), 4.12-3.97 (m, 2H), 3.96-3.85 (m, 1H), 3 (s,2H), 2.62 (d, 2H), 1.90 (s, 3H), 1.82-1.45 (m, 6H), 1.40-1.07 (m, 3H), 1.04-0.80 (m, 2H). MS (EI) for $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EXAMPLE 3(cw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(propylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.56 (s, 1H), 7.57 (dd, 1H), 7.37 (dd, 1H), 7.32 (m, 1H), 7.18 (m, 1H), 6.67 (m, 1H), 4.03 (d, 1H), 3.89 (m, 2H), 3.69 (d, 1H), 2.59 (s, 2H),

2.42 (t, 2H), 1.90 (s, 3H), 1.32 (m, 2H), 0.81 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

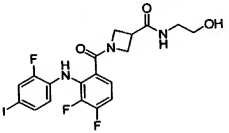
EXAMPLE 3(cx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.56 (s, 1H), 7.56 (dd, 1H), 7.36 (dd, 1H), 7.31 (m, 1H), 7.18 (m, 1H), 6.67 (m, 1H), 4.02 (d, 1H), 3.89 (m, 2H), 3.70 (d, 1H), 2.57 (s, 2H), 2.27 (d, 2H), 1.91 (s, 3H), 1.55 (m, 1H), 0.79 (d, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(cy). methyl (2xi)-2-deoxy-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-beta-D-arabino-hexopyranoside: ^{1}H NMR (400 MHz, d_4-methanol, ~3:1 mixture of anomers): δ 7.46 (d, 1H), 7.34 (d, 1H), 7.28 (m, 1H), 7.04 (q, 1H), 6.62 (m, 1H), 4.19-5.92 (m, 4H), 3.87-3.78 (m, 2H), 3.68 (m, 1H), 3.56-3.18 (m, 5H), 2.99-2.82 (m, 3H), 2.56 (m, 0.25H), 2.29 (m, 0.75H) MS (EI) for $C_{24}H_{27}F_3IN_3O_7$: 652 (M-H).

EXAMPLE 3(cz). 3-({[3-(diethylamino)propyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.24-4.16 (d, 1H), 4.11-3.99 (t, 2H), 3.92-3.85 (d, 1H), 3.10-3.02 (m, 8H), 2.99-2.96 (s, 2H), 2.92-2.87 (t, 2H), 1.93-1.87 (s, 3H), 1.27-1.20 (t, 6H); MS (EI) for $C_{24}H_{30}F_3IN_4O_2$: 591 (MH^+).

EXAMPLE 4

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide



[00335] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid (15 mg, 0.03 mmol), prepared using procedures similar to those in Example 1, in *N,N*-dimethylformamide (2.00 mL) was added HBTU (38 mg, 0.10 mmol). The mixture was stirred for 15

minutes at room temperature followed by the addition of 2-aminoethanol (3.6 μL, 0.06 mmol) and *N*-methylmorpholine (110 μL, 1.00 mmol). The mixture was allowed to stir at room temperature for 3 d, then diluted the mixture with chloroform (20 mL), and washed with water (30 mL). The aqueous phase was back extracted with chloroform (10 mL). The combined organic phases were dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by high pressure liquid chromatography to afford the title compound (9.20 mg, 58%) as the trifluoroacetic acid salt: ^{1}H NMR (400MHz, $CDCl_3$): 8.54 (s, 1H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 1H), 7.18-7.14 (m, 1H), 6.85-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.66 (br, 1H), 4.40-4.24 (br, 3H), 3.83-3.23 (br m, 7H), 1.18 (t, 3H); MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

[00336] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 4(a): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(3,4-dihydroxybutyl)azetidine-3-carboxamide: ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (s, 1H), 7.40 (dd, 1H), 7.31-7.35 (m, 1H), 7.14-7.18 (m, 1H), 6.78-6.84 (m, 1H), 6.59-6.65 (m, 1H), 6.14 (br s, 1H), 4.50-4.60 (m, 1H), 4.20-4.40 (m, 3H), 3.60-3.80 (m, 3H), 3.40-3.52 (m, 2H), 3.20-3.32 (m, 2H), 1.96 (br s, 1H), 1.18-1.28 (m, 2H). MS (EI) for $C_{21}H_{21}F_3IN_3O_4$: 562 (M-H).

EXAMPLE 4(b): *N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (dd, 1H), 7.33-7.31 (m, 1H), 7.17-7.13 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 5.50 (m, 1H), 4.57 (br, 1H), 4.29 (br m, 3H), 3.27 (m, 3H), 1.49 (m, 1H), 1.33 (m, 2H), 0.92 (t, 3H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+), 554 (MNa^+).

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-prop-2-en-1-ylazetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.54 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.17.7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 5.88-5.77 (m, 1H), 5.57 (br, 1H), 5.21-5.16 (m, 2H), 4.59 (br, 1H), 4.30 (br m, 3H), 3.9 (tt, 2H), 3.32-3.25 (m, 1H)); MS (EI) for $C_{20}H_{17}F_3IN_3O_2$: 516 (MH^+), 538 (MNa^+).

EXAMPLE 4(c): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidine-3-carboxamide: ^{1}H NMR

(400MHz, $CDCl_3$): 8.54 (s, 1H), 7.38 (dd, 1H), 7.33-7.30 (m, 1H),7.17-7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.57 (m, 1H), 5.55 (br s, 1H), 4.57 (br s, 1H), 4.28 (br m, 1H), 3..36-3.29 (m, 2H), 3.27- 3..20 (m, 1H), 1.15 (t, 3H); MS (EI) for $C_{19}H_{17}F_3IN_3O_2$: 504 (MH^+), 526 (MNa^+).

EXAMPLE 4(d): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide: ^1H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H),7.16-7.12 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.57 (br, 1H), 4.28 (br, 3H), 3.73 (t, 2H), 3.49-3.44 (m, 2H), 3.33-3.27 (m, 1H), 2.18 (br, 1H); MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

EXAMPLE 4(e): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-piperidin-1-ylethyl)azetidine-3-carboxamide: ^1H NMR (400MHz, $CDCl_3$): 11.28 (s, 1H), 8.55 (s, 1H), 7.38 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.82-6.76 (m, 1H), 6.63-6.58 (m, 1H), 4.42 (b, 1H), 4.26 (br m, 3H), 3.68 (br s, 2H), 3.58 (br d, 2H), 3.36 (br m, 1H)3.17 (br s, 1H), 2.63 (m, 4H), 1.92 (m, 5 H); MS (EI) for $C_{24}H_{26}F_3IN_4O_2$: 587 (MH^+).

EXAMPLE 4(f): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-phenylazetidine-3-carboxamide: ^1H NMR (400MHz, $CDCl_3$): 8.52 (s, 1H), 7.50 (d, 1H), 7.41-7.27 (m, 4H), 7.16 (m, 2H), 6.85-6.78 (m, 1H), 6.65-6.59 (m, 1H), 4.37 (br, 3H), 3.43 (m, 1H); MS (EI) for $C_{23}H_{17}F_3IN_3O_2$: 574 (MNa^+).

EXAMPLE 4(g): *N*-[2-(diethylamino)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide: ^1H NMR (400MHz, $CDCl_3$): 11.43 (s, 1H), 8.90 (s, 1H), 8.55 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.87-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.44-4.22 (m, 4H), 3.65 (m, 2H), 3.38 (m, 1H), 3.19-3.13 (m, 5H), 1.33(t, 6H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 575 (MH^+).

EXAMPLE 4(h): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-[(2,3-dihydroxypropyl)oxy]azetidine-3-carboxamide: MS (EI) for $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

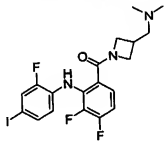
EXAMPLE 4(i): 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)azetidine-3-carboxamide: ^1H NMR (400 MHz, $CDCl_3$): 8.40 (br s, 1H), 7.35 (dd, 1H), 7.30 (br d, 1H), 7.16-7.09 (m, 1H), 6.89-6.76 (m, 2H), 6.58 (ddd, 1H), 4.58-4.40 (br, 1H), 4.27

(br t, 2H), 4.22-4.14 (br, 1H), 4.08-3.12 (m, 5H), 2.18-1.82 (br, 2H); MS (EI) for $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 4(j): 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-hydroxyazetidine-3-carboxamide: ^1H NMR (400 MHz, $CDCl_3$): 8.23-8.10 (b, 1H), 7.35-7.28 (m, 2H), 7.14-7.07 (m, 1H), 6.86-6.80 (m, 1H), 6.60-6.54 (m, 1H), 4.52-4.38 (b, 1H), 4.32-4.08 (m, 3H), 3.30-3.21 (m, 1H); MS (EI) for $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+).

EXAMPLE 5

6-({3-[dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline



[00337] A mixture of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid (196 mg, 0.41 mmol), prepared using procedures similar to those in Example 1, triethylamine (58 μL, 0.41 mmol), PyBOP (213 mg, 0.41 mmol) and sodium borohydride (48 mg, 1.24 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and the resultant residue was partitioned between 20% aqueous citric acid and ethyl acetate. The organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless residue that was purified by column chromatography. Eluting with 60% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 48 mg, 0.11 mmol (25%) of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol as a white solid. ^1H NMR (400 MHz, $CDCl_3$): 7.44 (d, 1H), 7.34 (d, 1H), 7.28-7.23 (m, 1H), 7.04-6.97 (m, 1H), 4.26-4.18 (m, 1H), 4.02-3.94 (m, 2H), 3.78-3.72 (m, 1H), 3.03 (d, 2H), 3.34 (s, 1H), 2.80-2.71 (m, 1H). MS (EI) for $C_{17}H_{14}F_3IN_2O$: 463 (MH^+).

[00338] A solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol (48 mg, 0.11 mmol),

1,4-diazabicyclo[2.2.2]octane (18 mg, 0.16 mmol) and methanesulfonyl chloride (10 μL, 0.13 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 15 minutes. The mixture was then partitioned between water and ethyl acetate. The organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless residue which was purified by column chromatography. Eluting with 70% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 28 mg, 0.05 mmol (47%) of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methyl methanesulfonate as a colorless residue which was immediately dissolved in ethylene glycol dimethyl ether (2 mL). To the solution was added dimethylamine (excess) and the solution was stirred in a seal tube at 50 °C for 15 hours. The reaction mixture was concentrated *in vacuo*, and the resultant residue was purified by preparative reverse phase HPLC. Isolated product was concentrated *in vacuo* to afford 12 mg, 0.02 mmol (40%) of 6-({3-[dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline acetate salt as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.54 (br s, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.33-7.28 (m, 1H), 7.18-7.12 (m, 1H), 6.70-6.64 (m, 1H), 4.18-4.12 (m, 1H), 3.99-3.76 (m, 1H), 3.52-3.47 (m, 1H), 2.52-2.48 (m, 1H), 2.39 (d, 2H), 1.85 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

[00339] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 5(a): 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-{[(1-methylethyl)amino]methyl}azetidin-1-yl)carbonyl]aniline: ^{1}H NMR (400 MHz, $CDCl_3$): 8.54 (s, 1H), 7.40 (dd, 1H), 7.31-7.33 (m, 1H), 7.11-7.15 (m, 1H), 6.76-6.82 (m, 1H), 6.58-6.64 (m, 1H), 4.23-4.30 (m, 2H), 3.90-4.00 (m, 1H), 3.76-3.84 (m, 1H), 2.69-2.85 (m, 4H), 1.05 (d, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 502 (M-H).

EXAMPLE 5(b): 2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}amino)ethanol: MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

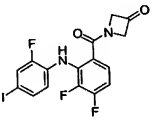
EXAMPLE 5(c): *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}ethane-1,2-diamine: MS (EI) for $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EXAMPLE 5(d): 6-({3-[dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline acetate salt: ^{1}H NMR (400 MHz, DMSO):

8.54 (br s, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.33-7.28 (m, 1H), 7.18-7.12 (m, 1H), 6.70-6.64 (m, 1H), 4.18-4.12 (m, 1H), 3.99-3.76 (m, 1H), 3.52-3.47 (m, 1H), 2.52-2.48 (m, 1H), 2.39 (d, 2H), 1.85 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

EXAMPLE 6

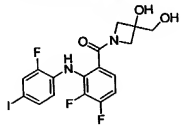
1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one



[00340] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (132 mg, 0.295 mmol)ures similar to those in Example 1, was dissolved in dichloromethane (8 mL) and cooled to 0 °C. Dess-Martin periodinane (187 mg, 0.441 mmol) was added and the mixture was stirred at ambient for 2 h. The mixture was quenched with saturated sodium bicarbonate solution: 10% sodium thiosulfate solution (1:1; 6 mL) and diluted with ethyl acetate. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 40-50% ethyl acetate in hexanes) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (122 mg, 0.273 mmol, 93% yield): ^1H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.44-7.38 (m, 1H), 7.36-7.32 (m, 1H), 7.27-7.20 (m, 1H), 6.86 (ddd, 1H), 6.64 (ddd, 1H), 4.94-4.93 (m, 4H); MS (EI) for $C_{16}H_{10}F_3IN_2O_2$: 447 (MH^+).

EXAMPLE 7

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol



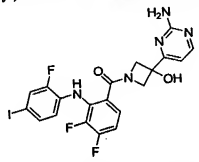
[00341] Methyl triphenylphosphonium bromide (508 mg, 1.42 mmol) was treated with potassium *tert*-butoxide (159 mg, 1.42mmol) in tetrahydrofuran (5 mL) at 0 °C for 10 minutes. 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (270 mg, 0.605 mmol), prepared using procedures similar to those described in Example 6, was dissolved in tetrahydrofuran (2 mL) and was added to the mixture. The mixture was stirred at ambient for 15 h and then the mixture was filtered and the filtrate was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ethyl acetate in hexanes) gave 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-methylideneazetidin-1-yl)carbonyl]aniline (57 mg, 0.128 mmol, 21% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (br s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.18-7.12 (m, 1H), 6.86-6.76 (m, 1H), 6.62 (ddd, 1H), 5.14-5.00 (br, 2H), 4.74 (br d, 4H); MS (EI) for $C_{17}H_{12}F_3IN_2O$: 445 (MH^+).

[00342] 2,3-Difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-methylideneazetidin-1-yl)carbonyl]aniline (56 mg, 0.126 mmol) and 4-methylmorpholine *N*-oxide (44 mg, 0.376 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (4 wt.% in water; 0.7 mL) was added. The solution was stirred at ambient for 4 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 80% ethyl acetate in hexanes) and then reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (17 mg, 0.036

mmol, 28% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.16-7.10 (m, 1H), 6.81 (ddd, 1H), 6.61 (ddd, 1H), 4.25-4.00 (m, 4H), 3.78 (s, 2H); MS (EI) for $C_{17}H_{14}F_3IN_2O_3$: 479 (MH^+).

EXAMPLE 8

3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00343] To a solution of 4-iodo-2-(methylthio)pyrimidine (2.00 g, 7.92 mmol) in tetrahydrofuran (4.00 ml) was added isopropylmagnesium chloride (815 mg, 7.92 mmol). The mixture was allowed to stir for 1 h at 0 °C, followed by the addition of 1,1-dimethylethyl 3-oxoazetidiene-1-carboxylate (1.64 g, 9.60 mmol), prepared using procedures similar to those described in Example 3. The reaction mixture was then allowed to warm to room temperature and stirred for 6h. The mixture was quenched with 1 N hydrochloric acid (10 mL) and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to afford 1,1-dimethylethyl 3-hydroxy-3-[2-(methylthio)pyrimidin-4-yl]azetidine-1-carboxylate (380 mg, 16%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 8.62-8.59 (d, 1H), 7.36-7.33 (d, 1H), 5.14-5.11 (s, 1H), 4.29-4.24 (d, 2H), 4.13-4.08 (d, 2H), 2.61-2.58 (s, 3H), 1.50-1.47 (s, 9H); MS (EI) for $C_{13}H_{19}N_3O_3S$: 298 (MH^+).

[00344] A solution of 1,1-dimethylethyl 3-hydroxy-3-[2-(methylthio)pyrimidin-4-yl]azetidine-1-carboxylate (480 mg, 1.62 mmol), and 3-chloroperoxybenzoic (558 mg, 3.23 mmol) acid in dichloromethane (25 mL) was stirred at room temperature for 22 h. The reaction mixture was quenched with a saturated solution of sodium thiosulfate and the pH adjusted to 7 with sodium carbonate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated

in vacuo. The resulting crude 1,1-dimethylethyl 3-hydroxy-3-[2-(methylsulfonyl)pyrimidin-4-yl]azetidine-1-carboxylate (524 mg, 98%) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 9.01-8.97 (d, 1H), 7.96-7.93 (d, 1H), 4.57-4.53 (s, 1H), 4.31-4.27 (d, 2H), 4.23-4.18 (d, 2H), 3.42-3.39 (s, 3H), 1.50-1.47 (s, 9H); MS (EI) for $C_{13}H_{19}N_3O_5S$: 330 (MH^+).

[00345] A solution of 1,1-dimethylethyl 3-hydroxy-3-[2-(methylsulfonyl)pyrimidin-4-yl]azetidine-1-carboxylate (215 mg, 0.652 mmol), and aqueous ammonia (7 mL, 28% solution) in dioxane (15 mL) within a sealed steel bomb cylinder was heated at 80°C for 4h. The mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane and a solution of saturated sodium carbonate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The resulting crude 1,1-dimethylethyl 3-(2-aminopyrimidin-4-yl)-3-hydroxyazetidine-1-carboxylate (140 mg, 100%) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.38-8.35 (d, 1H), 6.97-6.94 (d, 1H), 5.30-5.28 (s, 2H), 4.23-4.18 (d, 2H), 4.08-4.04 (d, 2H), 1.48-1.45 (s, 9H).

[00346] To a solution of 1,1-dimethylethyl 3-(2-aminopyrimidin-4-yl)-3-hydroxyazetidine-1-carboxylate (140 mg, 0.524 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (3 ml). The reaction mixture was stirred for 2h at room temperature. The mixture was concentrated *in vacuo*. The resulting crude 3-(2-aminopyrimidin-4-yl)azetidin-3-ol (87 mg, 100%) was used without further purification.

[00347] A solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (201 mg, 0.512 mmol), prepared using procedures similar to those described in US 7,019,033, 3-(2-aminopyrimidin-4-yl)azetidin-3-ol (87 mg, 0.52 mmol), benzotriazol-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (293 mg, 0.563 mmol) and *N,N*-diisopropylethylamine (270 uL, 2.82 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at room temperature for 20h. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by reverse phase HPLC to afford the title compound 3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (22 mg, 7%). ^{1}H NMR (400 MHz, CD_3OD): 8.23-8.20 (d, 1H), 7.48-7.43 (d, 1H), 7.35-7.32 (m, 2H), 7.09-7.00 (m, 1H),

6.88-6.84 (d, 1H), 6.70-6.63 (t, 1H), 4.59-4.54 (d, 1H), 4.45-4.40 (d, 1H), 4.23-4.18 (d, 1H), 3.04-3.99 (t, 1H); MS (EI) for $C_{20}H_{15}F_3IN_5O_2$: 542 (MH^+).

[00348] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 8(a): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyridin-2-ylazetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 8.47 (m, 1H), 7.80 (m, 1H), 7.65 (d, 1H), 7.44 (m, 1H), 7.33 (m, 3H), 7.04 (m, 1H), 6.65 (m, 1H), 4.61 (d, 1H), 4.44 (d, 1H), 4.29 (d, 1H), 4.12 (d, 1H). MS (EI) for $C_{21}H_{15}F_3IN_3O_2$: 526 (MH^+).

EXAMPLE 8(b): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-yl)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7.42 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.02 (m, 3H), 6.63 (m, 1H), 4.65 (d, 1H), 4.42 (d, 1H), 4.33 (d, 1H), 4.16 (d, 1H). MS (EI) for $C_{19}H_{14}F_3IN_4O_2$: 515 (MH^+).

EXAMPLE 8(c): 3-(1*H*-benzimidazol-2-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7.55 (br s, 2H), 7.42 (m, 2H), 7.33 (m, 1H), 7.23 (m, 2H), 7.04 (m, 1H), 6.65 (m, 1H), 4.76 (d, 1H), 4.57 (d, 1H), 4.43 (d, 1H), 4.25 (d, 1H). MS (EI) for $C_{23}H_{16}F_3IN_4O_2$: 565 (MH^+).

EXAMPLE 8(d): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(5-methyl-1*H*-imidazol-2-yl)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7.41 (m, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.02 (m, 1H), 6.67 (br s, 1H), 6.63 (m, 1H), 4.63 (d, 1H), 4.39 (d, 1H), 4.30 (d, 1H), 4.13 (d, 1H), 2.18 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 8(e): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-prop-2-en-1-ylazetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8.47 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.15-7.10 (m, 1H), 6.81 (ddd, 1H), 6.62 (ddd, 1H), 5.84-5.72 (m, 1H), 5.27-5.20 (m, 2H), 4.22-3.94 (m, 4H), 2.52 (d, 2H), 2.25 (s, 1H); MS (EI) for $C_{19}H_{16}F_3IN_2O_2$: 489 (MH^+).

EXAMPLE 8(f): 3-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]propane-1,2-diol: ^1H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.16-

7.10 (m, 1H), 6.82 (ddd, 1H), 6.61 (ddd, 1H), 4.31-3.91 (m, 5H), 3.68 (br d, 1H), 3.54-3.49 (m, 1H), 2.01-1.80 (m, 2H); MS (EI) for $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EXAMPLE 8(g): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethenylazetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8.48 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.17-7.11 (m, 1H), 6.81 (ddd, 1H), 6.62 (ddd, 1H), 6.15 (dd, 1H), 5.39 (d, 1H), 5.28 (d, 1H), 4.30-4.10 (m, 4H); MS (EI) for $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

EXAMPLE 8(h): 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethane-1,2-diol hydrochloride: ^1H NMR (400 MHz, d_6-DMSO): 8.66 (d, 1H), 7.58 (dd, 1H), 7.38 (d, 1H), 7.33-7.27 (m, 1H), 7.17 (q, 1H), 6.74-6.65 (m, 1H), 4.50-3.58 (br, 3H), 4.29 (dd, 1H), 4.14 (dd, 1H), 3.87 (t, 1H), 3.66 (t, 1H), 3.56-3.32 (m, 3H); MS (EI) for $C_{18}H_{16}F_3IN_2O_4$: 509 (MH^+).

EXAMPLE 8(i): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethylazetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8.23 (br s, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.15-7.10 (m, 1H), 6.85-6.79 (m, 1H), 6.64-6.58 (m, 1H), 4.14-3.94 (m, 4H), 1.78 (q, 2H), 0.96 (t, 3H); MS (EI) for $C_{18}H_{16}F_3IN_2O_2$: 477 (MH^+).

EXAMPLE 8(j): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-methylazetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8.31 (br s, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.15-7.11 (m, 1H), 6.85-6.78 (m, 1H), 6.65-6.59 (m, 1H), 4.24-4.04 (m, 4H), 1.55 (s, 3H); MS (EI) for $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

EXAMPLE 8(k): 3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 8.22-8.20 (d, 1H), 7.48-7.43 (d, 1H), 7.38-7.30 (m, 1H), 7.09-7.01 (q, 1H), 6.88-6.84 (d, 1H), 6.70-6.61 (t, 1H), 4.59-4.54 (d, 1H), 4.44-4.39 (d, 1H), 4.23-4.19 (d, 1H), 4.05-3.99 (d, 1H), 3.90-3.81 (d, 1H), 1.99-1.97 (s, 3H); MS (EI) for $C_{20}H_{15}F_3I\ N_5O_2$: 542 (MH^+).

EXAMPLE 8(m): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-pyrrol-2-yl)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7.37 (dd, 1H), 7.31-7.23 (m, 2H), 7.07-6.97 (m, 1H), 6.73-6.68 (m, 1H), 6.65-6.56 (m, 1H), 6.06-5.98 (m, 2H), 4.49-4.40 (m,1H), 4.32-4.18 (m, 2H), 4.15-88-4.07 (m, 1H). MS (EI) for $C_{20}H_{15}F_3IN_3O_2$: 514 (MH^+)